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HEARINGS

BEFORE A

SUBCOMMITTEE OF THE COMMITTEE ON GOVERNMENT OPERATIONS HOUSE OF REPRESENTATIVES

NINETY-NINTH CONGRESS

FIRST SESSION

JULY 24 AND 25, 1985

Printed for the use of the Committee on Government Operations

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THE REGULATION OF ANIMAL DRUGS BY THE FOOD AND DRUG ADMINISTRATION

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THE REGULATION OF ANIMAL DRUGS BY THE FOOD AND DRUG ADMINISTRATION

WEDNESDAY, JULY 24, 1985

House of Representatives,
Intergovernmental Relations
and Human Resources Subcommittee
of the Committee on Government Operations,
Washington, DC.

The subcommittee met, pursuant to notice, at 9:35 a.m., in room 2154, Rayburn House Office Building, Hon. Ted Weiss (chairman of the subcommittee) presiding.

Present: Representatives Ted Weiss and Robert S. Walker.

Also present: James R. Gottlieb, staff director; Daniel W. Sigelman, counsel; Gwendolyn S. Black, secretary; and Martha Morrison, minority professional staff, Committee on Government Operations.

OPENING STATEMENT OF CHAIRMAN WEISS

Mr. Weiss. Good morning. The subcommittee will come to order.

Today the subcommittee begins 2 days of oversight hearings on the Food and Drug Administration's (FDA's) regulation of powerful animal drugs that permeate the Nation's supply of meat, milk, and eggs.

FDA's enforcement of the Nation's animal drug safety laws affects the quality of life for all Americans. The safety, quality, and wholesomeness of our food supply vitally depend on decisions made by some of those who will appear before this subcommittee over the next 2 days.

FDA's Center for Veterinary Medicine (CVM), which is responsible for regulating drugs administered to animals raised for human consumption, has not been the subject of comprehensive congressional oversight for more than a decade. The Chair intends, therefore, to examine a wide array of regulatory issues in an attempt to determine whether CVM has been vigorously carrying out its mandate to prevent chemical contamination of the food chain.

I regret to report that preliminary findings by the subcommittee staff indicate fundamental shortcomings in FDA's ability and willingness to regulate the development, use, and marketing of potent drugs which persist in animal-derived food. Among the questions we intend to explore are:

First, why is the animal drug marketplace overwhelmingly dominated by drugs whose safety and efficacy have never been approved by FDA?

Second, why is FDA apparently unable to control widespread illegal distribution of toxic veterinary prescription drugs?

Third, why is our Government unable to monitor for most of the animal drugs leaving residues in our food?

Fourth, why hasn't FDA removed potentially unsafe new animal drugs from the market?

Fifth, has the pressure to speed the approval of new animal drugs compromised FDA's ability to assure the safety of our food supply?

Our witnesses over the next 2 days will be representatives from the Food and Drug Administration, led by Dr. Lester M. Crawford, who is the Director of FDA's Center for Veterinary Medicine.

The subcommittee, as always, competes with other activities ongoing on the floor and in other committees and subcommittees of the House. From time to time, Members of the subcommittee will be coming in and leaving. I am sure that our witnesses will understand that that is forced upon us by the heavy schedule that the House is maintaining at this point.

Dr. Crawford, would you and your associates please come forward? Because it is customary for this subcommittee to have witnesses sworn in, please remain standing. Before we do that, would you and all of your associates please identify yourselves for the record?

Dr. CRAWFORD. I am Lester M. Crawford, Director of the Center for Veterinary Medicine.

Mr. DOLS. I am Thomas J. Dols, supervisory chemist in the Division of Surveillance.

Dr. GUEST. I am Gerald B. Guest, Deputy Director, Center for Veterinary Medicine.

Mr. SHANE. I am Clifford D. Shane, the regional director, region VII, Food and Drug Administration.

Mr. WEISS. Thank you very much, gentlemen.

Do you swear that the testimony you are about to give is the truth, the whole truth, and nothing but the truth? Let the record show that the witnesses responded in the affirmative.

Any other witnesses or staff people who will be called on to provide supportive testimony in the course of the hearings will also be asked to be sworn in.

Dr. Crawford, on behalf of the subcommittee, I want to express our appreciation to you and your colleagues for your appearance today. We look forward to your testimony. You may read your entire prepared statement or you may summarize it. In any case, the entire prepared statement will be made part of the hearing record. In addition, we will also be entering, without objection, a number of documents into the hearing record, and if you wish to have any specific document placed in the record as we go along, please just let us know.

Dr. Crawford, we are ready for your statement.

STATEMENT OF LESTER M. CRAWFORD, D.V.M., Ph.D., DIRECTOR, CENTER FOR VETERINARY MEDICINE, FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY DR. GERALD B. GUEST, DEPUTY DIRECTOR; THOMAS J. DOLS, SUPERVISORY CHEMIST, DIVISION OF SURVEILLANCE; AND CLIFFORD D. SHANE, REGIONAL DIRECTOR, REGION VII

Dr. CRAWFORD. Thank you very much. Mr. Chairman, we appreciate the opportunity to be here today. We will summarize the statement, with your permission.

We are proud of our program and its accomplishments over the last several years, including an improved animal drug approval process which gives priority to breakthrough and orphan-type products; second, efforts to restrict or remove potentially dangerous products from the markets, such as DES and chloramphenicol; third, an increased level of regulatory actions to protect animal and human health; an expanded leadership role in international veterinary medical affairs; a greater number of research projects aimed at improving our ability to detect drug residues in food-producing animals; and the establishment of a Veterinary Medical Advisory Committee to provide us with expert counsel on important health issues.

Mr. Chairman, under the heading of overall responsibility, the Center regulates the interstate marketing and use of animal drugs and feeds. We review applications for new products to assure they are safe and effective for animals and safe for consumers of food animal products in the environment.

Once products are approved, we monitor the activities of manufacturers, food producers, and veterinarians to determine that products are being safely manufactured and are used in accordance with labeling. In addition, we perform basic research on important problems that are not being studied in the private sector. The Center often must respond to emergencies that threaten animal health or human health. These crises require prompt and appropriate responses. For example, when faced with outbreaks of serious diseases for which no approved drug is available, we sometimes must consider permitting the limited marketing of animal drugs during the investigational phase. In such cases, we must carefully weigh the risks versus the benefits before any decision is made.

Finally, because the United States has assumed a central role in the international trade of animal products, the Center is charged with facilitating global cooperation in the veterinary field. In 1983, for example, we organized the first International Technical Consultation on Veterinary Drug Registration. More recently, the World Health Organization has selected the United States as a host country for an important new committee on veterinary medicine.

Of all our responsibilities, perhaps the most important is the review of new animal products. Our challenge is to carefully review each product for safety and effectiveness without impeding or slowing the development of important new drugs and other products which can combat animal diseases or expand the food supply.

The Center's priority system for evaluating new drug applications is one way we attempt to deal with this challenge. Veterinary drugs, like human drugs, are ranked according to their potential value. Those with the greatest potential value, for instance, breakthrough drugs aimed at diseases for which no drug has been developed, are given the highest review priority. Drugs which promise some potential advance over existing therapies are given second priority. Special consideration is also given to minor-use animal drugs, the veterinary equivalent of human orphan drugs.

CVM has launched several initiatives to stimulate the development of minor-use drugs. These include a new regulation which expedites review of data on minor-use drugs and a broad based program of support for extramural and intramural research on minor-use drugs. The research program, which depends upon close liaison with the United States Department of Agriculture, will strengthen the scientific data base which underlies FDA's regulatory policies and decisions.

As with human drugs, before a new animal drug application or NADA is submitted, the drug sponsor, usually a manufacturer, must conduct laboratory and clinical investigations to establish safety and efficacy. If the drug is to be tested in food-producing animals, the drug sponsor is required to obtain approval from the Agency if the sponsor intends to market food from the animals in the study.

Inspections of laboratory and clinical animal drug studies are conducted by the Agency's Bioresearch Program to ensure adequate research facilities and procedures that comply with good laboratory practice or clinical investigator regulations. When FDA inspectors learn that an investigational drug may be unsafe for use in food-producing animals or that the drug is being distributed for other than valid research purposes, the Agency may order an end to the investigation. In those cases where conclusive evidence points to illegal practices, for instance, commercialization of an investigational drug, FDA will take appropriate enforcement action.

The results of most animal drug investigations are eventually submitted to CVM as part of a new animal drug application. One burden for the sponsor is to demonstrate in the application that any drug residues remaining in a food-producing animal after withdrawal of the drug prior to slaughter must pose no threat to the safety of consumers. The Agency has developed stringent standards for determining the safety of animal drug residues. An application must contain data on the toxicity of a drug in laboratory animals. These studies must address potential toxicological affects and potential carcinogenic, reproductive, or teratogenic effects. The submitted data also must describe how the drug is metabolized by animals, the kinds and amounts of remaining residues, and a laboratory assay method that can detect such residues in meat or poultry products.

Over the past 5 years, the Center has developed a number of new scientific guidelines and updated existing ones to assist the industry in meeting the drug review standards the Agency requires. These guidelines have helped clarify our requirements and made it easier for industry to comply with them. We also have established just recently a Veterinary Medical Advisory Committee to assist us in making better and more informed judgments on safety and efficacy. We believe that this committee will be invaluable in providing us with expert counsel on difficult and complex health issues.

Under the area of post-marketing surveillance, Mr. Chairman, animal drugs, like human drugs, must go through a stringent, preclearance process before being approved. They can, nevertheless, cause problems once they are marketed. New drug applications are by necessity approved on the basis of relatively limited data selected from limited numbers of animals. Therefore, certain adverse affects may not be apparent until the drug is widely marketed and administered to large numbers of animals, in different geographical areas, under various field conditions by both careful and careless users. Post-marketing surveillance is critical to learn of these possible affects. Surveillance is accomplished through reviews of special and periodic reports of experience that must be submitted to FDA following approval of a new animal drug product. These reports are known as Drug Experience Reports, or DERs, and contain information on package labeling; advertising; quantities marketed; adverse drug reactions, including any failure of the drug to perform as expected; and other information that can be used as a basis for determining whether the drug product continues to be safe and effective.

We cooperate with both the veterinary profession and individual veterinarians to obtain information on adverse drug experience. We distribute special reporting forms to simplify and facilitate voluntary reporting by practitioners. For the past several years, we have provided and publicized our Adverse Reaction Hotline, which is available for veterinarians to call collect, to submit information on adverse drug experience.

Other sources of adverse reaction and injury reports also are utilized. We carefully weigh the data generated by our adverse reaction reporting system to determine what actions, if any, may be required. Quite often, we require that warnings or contraindications be added to the drug labeling. Very serious adverse reactions to significant numbers of animals or humans who have consumed animal products could lead to a severe restriction or total ban of the drug in question.

Enforcement. Although most products that clear the hurdles of our pre-market approval system prove to be safe for their intended uses, problems can still occur with the overuse or misuse of these products. Our compliance and enforcement activities, which we coordinate with FDA's field operation, are aimed at preventing or reducing these and other problems. To achieve uniform and effective compliance, CVM develops written compliance programs and compliance policy guides to deal with the various violations we encounter. These provide both general and specific guidance to the FDA field offices responsible for conducting surveillance of the regulated industries and recommending enforcement actions to headquarters offices.

The majority of recommended actions submitted by the field and reviewed by CVM are approved. Further, the Agency has a procedure for review of recommendations which have been disapproved. Such regulatory actions which may be taken cover the entire range of our statutory authorities, including regulatory letters, seizures, injunctions, and prosecutions. To better promote industry compliance with our laws and regulations, we also utilize public information and educational programs. These programs are not intended to replace regulatory activities; rather, they are designed to bring into compliance firms which may be in violation of the act through simple mistakes or ignorance, and thereby permit us to concentrate our regulatory efforts on those violators who are willfully out of compliance.

One recent example of the complex regulatory problem that has involved using both regulatory actions and public information and education programs is our effort to combat the illegal sale of prescription veterinary drugs. Surveillance by our field offices and information received from outside the Agency had shown that there is an abuse of the restrictions imposed by the veterinary prescription legend and that it is a national problem. What this means is that veterinary prescription drugs are being sold by distributors directly to lay persons, without a prescription or other order of a licensed veterinarian. To combat these illegal activities, the Agency has developed a comprehensive initiative which involves enforcement actions, information, and educational activities and cooperative efforts with trade and professional associations and with the States. FDA has taken a large number of enforcement actions to control the illegal distribution of prescription veterinary drugs. The actions have been taken against peddlers, mail order operations, distributors, retailers, and veterinary clinics. We also participated in a public forum in the State of Iowa in which this program was highlighted and discussed constructively with veterinarians. We believe that these actions will help bring this problem under control.

In enforcement, as in other areas, we must set priorities to best utilize our limited resources. Problems which may present a risk to human health must be given first priority. Animal health problems, of course, rank second, and economic problems last. In this connection, there are many animal drugs on the market today, mostly older drugs used to treat horses or pets which have never been approved by the Food and Drug Administration.

As we encounter unapproved drugs being used in food-producing animals, because there could be a risk to humans from the use of these drugs, we take appropriate regulatory action against the drug or the parties involved. When drugs appear to pose no risk to humans or animals, based on the best available evidence, we may take only minor action, such as labeling or formulation changes, because our resources are needed to deal with more serious problems.

Finally, in the area of research, let me say that pre-clearance and post-marketing decisionmaking in CVM must be supported by the best science. We must always assure ourselves that our actions are well founded. In those areas of responsibility where we continue to have less than adequate knowledge, we must take steps to increase the knowledge base through well conceived research. We encourage the regulated industry to do such research, but there are areas where industry and even academia are not conducting studies.

It is in these areas that the Center is concentrating its research efforts. These efforts are vitally important to our regulatory mission. Over the last several years, CVM has been engaged in a number of research projects aimed at improving animal and human safety. These include: A project aimed at determining the extent to which alfatoxin, a naturally occurring toxin in corn and other vital animal feeds, are transferred to the milk of dairy cattle;

A study of sulfamethazine in veal calves to determine whether current uses and withdrawal methods result in safe levels of residues in edible tissues. We are concerned, for example, that the use of this commonly used anti-bacterial agent in very young or bob veal calves may result in unsafe residue levels;

A study to develop a multi-residue assay for benzimidazoles—these are a class of drugs that are used to treat parasites in animals and are widely used in a variety of food-producing animals. A method to test for residues of all these drugs would greatly aid USDA and also FDA drug residue enforcement efforts;

An investigation of the interaction of various drugs and nutrients used in food-producing animals to determine whether diets affect the efficiency of certain growth promotion drugs;

Finally, the development of a multi-residue method to detect violative levels of aminoglycoside antibiotics which are used in several types of food-producing animals. Like our study on the benzimidazoles noted above, a multi-residue method for these drugs would aid USDA and FDA in enforcing drug residue limits.

In conclusion, Mr. Chairman, FDA is proud of its achievements over the last several years. We have worked in a number of areas, including new product approval, post-marketing surveillance, enforcement, and research to help assure the safety and efficacy of veterinary products. We try to use our limited resources to deal with problems that have the greatest impact on human and animal health. Although difficult problems still face us, we feel we have made substantial progress in fulfilling our basic mission. We will continue to assure that Americans enjoy the safest and most nutritious food supply in the world today.

This concludes my statement. My colleagues and I will be happy to answer questions that you might have.

[The prepared statement of Dr. Crawford follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT BY

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FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON INTERGOVERNMENTAL RELATIONS AND HUMAN RESOURCES

COMMITTEE ON GOVERNMENT OPERATIONS

HOUSE OF REPRESENTATIVES

JULY 24, 1985

FOR RELEASE ONLY UPON DELIVERY

Mr. Chairman:

I appreciate this opportunity to discuss the efforts of the Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM) to assure the safety and efficacy of animal drugs and feeds.

We are proud of our program and its accomplishments over the last several years including:

-- An improved drug approval process which gives priority to "breakthrough" and orphan type products;

-- Efforts to restrict or remove potentially dangerous products from the markets such as DES and chloramphenical;

-- An increased level of regulatory actions to protect animal and human health;

-- An expanded leadership role in international veterinary medicine affairs;

-- A greater number of research projects aimed at improving our ability to detect drug residues in food-producing animals; and

-- The establishment of a Veterinary Medicine Advisory Committee to provide us with expert council on important health issues.

Overall Responsibilities

The Center regulates the interstate marketing and use of animal drugs and feeds. We review applications for new products to assure they are safe and effective for animals, and safe for consumers of food animal products and the environment. Once products are approved, we monitor the activities of manufacturers, food producers, and veterinarians to determine that products are being safely manufactured and used in accordance with their labeling. In addition, we perform basic research on important problems that are not being studied in the private sector.

The Center often must respond to emergencies that threaten animal health or human health. These crises require prompt and appropriate responses. For example, when faced with outbreaks of serious diseases for which no approved drug is available, we sometimes must consider permitting the limited marketing of animal drugs during the investigational phase. In such cases, we must carefully weigh the risks versus the benefits before any decision is made.

Finally, because the United States has assumed a central role in the international trade of animal products, the Center is charged with facilitating global cooperation in the veterinary field. In 1983, for example, we organized the first International Technical Consultation on Veterinay Drug Registration. More recently, the World Health Organization (WHO) has selected the United States as the host country for an important new committee on Veterinary Medicine.

New Product Review

Of all our responsibilities, perhaps the most important is the review of new animal products. Our challenge is to carefully review each product for safety and effectiveness without impeding or slowing the development of important new drugs and other products which can combat animal diseases or expand the food supply.

The Center's priority system for evaluating new drug applications is one way we attempt to deal with this challenge. Veterinary drugs, like human drugs, are ranked according to their potential value. Those with the greatest potential value (i.e., "breakthrough" drugs aimed at diseases for which no drug has been developed) are given the highest review priority. Drugs which promise some potential advance over existing therapies are given second priority.

Special consideration is also given to "minor use" animal drugs (the veterinary equivalent of human "orphan" drugs). CVM has launched several initiatives to stimulate the development of minor use drugs. These include a new regulation which expedites review of data on minor use drugs, and a broad-based program of support for extramural and intramural research on minor use drugs. The research program, which depends upon close liaison with the United States Department of Agriculture (USDA), will strengthen the scientific data base which underlies FDA regulatory policies and decisions.

As with human drugs, before a new animal drug application (NADA) is submitted, the drug sponsor (usually a manufacturer) must conduct laboratory and clinical investigations to establish safety and efficacy. If the drug is to be tested in food-producing animals, the drug sponsor is required to obtain approval from the Agency if the sponsor intends to market food from the animals in the study.

Inspections of laboratory and clinical animal drug studies are conducted by the Agency's bioresearch program to ensure adequate research facilities and procedures that comply with Good Laboratory Practice or Clinical Investigator regulations. When FDA inspectors learn that an investigational drug may be unsafe for use in food-producing animals, or that the drug is being distributed for other than valid research purposes, the Agency may order an end to the investigation. In those cases where conclusive evidence points to illegal practices (e.g., commercialization of an investigational drug) FDA will take appropriate enforcement action.

The results of most animal drug investigations are eventually submitted to CVM as part of an new animal drug application. One burden for the sponsor is to demonstrate in the application that any drug residues remaining in a food-producing animal after withdrawal of the drug prior to slaughter must pose no threat to the safety of consumers. The Agency has developed stringent standards for determining the safety of animal drug residues. An application must contain data on the toxicity of the drug in laboratory animals. These studies must address potential toxicological effects and potential for carcinogenic, reproductive, or teratogenic effects. The submitted data also must describe how the drug is metabolized by animals, the kinds and amounts of remaining residues, and a laboratory assay method that can detect such residues in meat or poultry products.

Over the past five years, the Center has developed a number of new scientific guidelines and updated existing ones to assist the industry in meeting the drug review standards the Agency requires. These guidelines have helped clarify our requirements, and made it easier for industry to comply with them.

We have also established, just recently, a Veterinary Medicine Advisory Committee to assist us in making better and more informed judgments on safety and efficacy. We believe that this committee will be invaluable in providing us with expert counsel on difficult and complex health issues.

Post-Marketing Surveillance

Even though animal drugs, like human drugs, must go through a stringent preclearance process before being approved, they can, nevertheless, cause problems once they are marketed. New drug applications are by necessity approved on the basis of relatively limited data collected from limited numbers of animals. Therefore, certain adverse effects may not be apparent until the product is widely marketed and administered to large numbers of animals, in different geographical areas, under various field conditions, by both careful and careless users. Post-marketing surveillance is critical to learn of these possible effects.

Surveillance is accomplished through reviews of special and periodic reports of experience that must be submitted to FDA following approval of a new animal drug product. These reports are known as drug experience reports (DERs) and contain information on package labeling, advertising, quantities marketed, adverse drug reactions including any failure of the drug to perform as expected, and other information that can be used as a basis for determining whether the drug product continues to be safe and effective.

We cooperate with both the veterinary profession and individual veterinarians to obtain information on adverse drug experience. We distribute special reporting forms to simplify and facilitate voluntary reporting by practitioners. For the last several years, we have provided and publicized our "Adverse Reaction Hot Line" which is available for veterinarians to call collect to submit information on adverse drug experience. Other sources of adverse reaction and injury reports are also utilized.

We carefully weigh the data generated by our adverse reaction reporting systems to determine what actions, if any, may be required. Quite often we require that warnings or contraindications be added to the drug labeling. Very serious adverse reactions to significant numbers of animals or humans who have consumed animal products could lead to a severe restriction or total ban of the drug in question.

Enforcement

Although most products that clear the hurdles of our premarket approval system prove to be safe for their intended uses, problems can still occur with the overuse or misuse of these products. Our compliance and enforcement activities, which we coordinate with FDA's field operation, are aimed at preventing or reducing these and other problems. To achieve uniform and effective compliance, CVM develops written compliance programs and compliance policy guides to deal with the various violations we encounter. These provide both general and specific guidance to the FDA field offices responsible for conducting surveillance of the regulated industries and recommending enforcement actions to headquarters offices.

The majority of recommended actions submitted by the field and reviewed by CVM are approved. Further, the Agency has a procedure for review of recommendations which have been disapproved. Such regulatory actions which may be taken cover the entire range of our statutory authorities include regulatory letters, seizures, injunctions and prosecutions.

To promote better industry compliance with our laws and regulations, we also utilize public information and education programs. These programs are not intended to replace regulatory activities; rather they are designed to bring into compliance firms which may be in violation of the Act through simple mistakes or ignorance and, thereby, permit us to concentrate our regulatory efforts on those violators who are willfully out of compliance.

One recent example of a complex regulatory problem that has involved using both regulatory actions and public information and education programs is our effort to combat the illegal sale of prescription veterinary drugs. Surveillance by our field offices and information received from outside the Agency has shown that there is an abuse of the restrictions imposed by the veterinary prescription legend, and that it is a nationwide problem. What this means is that veterinary prescription drugs are being sold by distributors directly to lay persons without a prescription or other order of a licensed veterinarian. To combat these illegal activities, the Agency has developed a comprehensive initiative which involves enforcement actions, information/education activities, and cooperative efforts with trade and professional associations and with the States.

FDA has taken a large number of enforcement actions to control the illegal distribution of prescription veterinary drugs. The actions have been taken against peddlers, mail-order operations, distributors, retailers, and veterinary clinics. We also participated in a public forum in the State of Iowa at which this problem was highlighted and discussed constructively with veterinarians. We believe that these actions will help bring this problem under control.

In enforcement, as in other areas, we must set priorities to best utilize our limited resources. Problems which may present a risk to human health must be given first priority. Animal health problems, of course, rank second and economic problems last.

In this connection, there are many animal drugs on the market today--mostly older drugs used to treat horses or pets--which have never been approved by FDA. As we encounter unapproved drugs being used in food-producing animals, because there could be a risk to humans from the use of these drugs, we take appropriate regulatory action against the drug or the parties involved. When drugs appear to pose no risk to human or animals, based on the best available evidence, we may take only minor actions such as labeling or formulation changes because our resources are needed to deal with more serious problems.

Research

Preclearance and post-marketing decisionmaking in CVM must be supported by the very best science. We must always assure ourselves that our actions are well founded. In those areas of responsibility where we continue to have less than adequate knowledge, we must take steps to increase the knowledge base through well-conceived research.

We encourage the regulated industry to do such research but there are areas where industry and even academia are not conducting studies. It is in these areas that the Center is concentrating its research efforts. These efforts are vitally important to our regulatory mission.

Over the last several years CVM has been engaged in a number of research projects aimed at improving animal and human safety. These include:

-- A project aimed at determining the extent to which aflatoxin, a naturally occurring toxin, in corn and other vital animal feeds are transferred to the milk of dairy cattle;

-- A study of sulfamethazine in veal calves to determine whether current uses and withdrawal methods result in safe levels of residues in edible tissues. We are concerned, for example, that the use of this commonly used antibiotic in very young or "bob veal" calves may result in unsafe residue levels;

-- A study to develop a multi-residue assay for benzimidazoles drugs (a class of anti-parasitic drugs) which are widely used in a variety of food-producing animals. A method to test for residues of all of these drugs would greatly aid USDA and FDA drug residue enforcement efforts;

- An investigation of the interaction of various drugs and nutrients used in food-producing animals to determine whether diets effect the efficiency of certain growth promotion drugs.

- The development of a multi-residue method to detect violative levels of aminoglycoside antibiotics which are used in several types of food-producing animals. Like our study on the benzimidazoles drugs noted above, a multi-residue method for these drugs would aid USDA and FDA efforts to enforce drug residue limits.

Conclusion

In conclusion, Mr. Chairman, FDA is proud of its achievements over the last several years. We have worked in a number of areas including new product approval, post-marketing surveillance, enforcement and research to help assure the safety and efficacy of veterinary products. We try to use our limited resources to deal with problems that have the greatest impact on human and animal health. Although difficult problems still face us, we feel we have made substantial progress in fulfilling our basic mission. We will continue to assure that Americans enjoy the safest and most nutritious food supply in the world today.

This concludes my statement, Mr. Chairman. If you or members of the Subcommittee have any questions, I will be happy to answer them.

Mr. WEISS. Thank you very much, Dr. Crawford. Perhaps the place to start is right where you left off. You just stated that the basic mission of FDA's Center for Veterinary Medicine is to assure that Americans enjoy the safest and most nutritious food supply in the world today. How important, in your judgment, is the regulation of the clinical evaluation, distribution, and use of animal drugs to the health, safety, and general well-being of the consuming public?

Dr. CRAWFORD. It is very important. It is very important because our mission, Mr. Chairman, is understandably complex. We must predict these drugs before they are approved to go on the market. And, as you know, they are tested under field conditions to some extent, but the initial testing is in laboratory animals in a fixed control setting, and we must be able to predict what will happen to the drug once it is used commercially, obviously, in much larger numbers of animals.

And then, finally, it is up to us, working with FDA and sometimes with EPA, to be sure that misuse does not result in residues or harm to man or to animals. And in so doing, we must police the 50 States and the possessions of the United States.

Mr. WEISS. And what happens if, in fact, residues of some of these drugs, which are found to be hazardous, remain in animals consumed by humans?

Dr. CRAWFORD. Let me answer in the general sense and, also, with an example, if I may.

First, the way that the thing happens is that FDA, as you know, approves the drug. And then we work out with the firm and with USDA an analytical method to test for the drug in tissues that will be consumed by human beings. So this chemical method, once it is approved and once we are assured that the drug is safe and effective, we will allow marketing.

USDA then, because of the fact that they must, by law, inspect each and every animal that is consumed for human food, if they are red meat-producing animals or poultry, and, therefore, are already in the plants, take samples from a random number of carcasses or also from carcasses that they suspect of being contaminated. They analyze the sample to see if a wide range of residues may be present. They report back to us, that is, the FDA, the finding of any suspicious or frankly illegal residues.

We then attempt to trace back to the perpetrator of the illegal residue the problem. Now, as you would know, in many cases, or in most cases, this occurs infrequently. So we may get a residue of a certain drug and then our goal is to go back and find out who willfully or accidentally contaminated that segment of the American food supply.

Mr. WEISS. Ingesting those residues, then, may subject consumers to whatever damage or hazard that those chemicals can cause. Is that right?

Dr. CRAWFORD. Yes, Mr. Chairman; that is correct.

Mr. WEISS. So that people who then consume meat or poultry or eggs, which have some of these residues, may themselves then develop cancer or some other condition. Is that correct?

Dr. CRAWFORD. That is correct.

Mr. WEISS. Could you describe the Center for us? How it is organized, what are its staffing levels and what is its budget?

Dr. CRAWFORD. Yes. We are organized, basically, in keeping with our statutory responsibility. We have a director who oversees the overall operations of the Center. In this sense, the Center for Veterinary Medicine is similar to its counterparts; Food Safety and Applied Nutrition, Devices and Radiological Health; and Drugs and Biologics. There are four operation centers.

The Center director, which is me, reports to the Commissioner of FDA. There is a deputy director of the Center for Veterinary Medicine, who is the chief line operating officer. That is Dr. Guest, who is to my right and to your left. Then under Dr. Guest are three associate directors, and they head up the operating offices within the Center for Veterinary Medicine. There is an associate director for new animal drug evaluation. And in that area, those individuals review drugs for the marketplace. They are charged with premarket approval. In all but the most unusual approvals, those circumstances are handled within that office. They have delegated authority to deal with the approval of new animal drugs.

The second office under Dr. Guest within the Center is headed by the associate director for Surveillance and Compliance. These individuals in that particular unit are charged with what happens with the drug once it gets into the marketplace, that is, surveillance and compliance. They are also charged with dealing with drugs that may not be approved, that are either smuggled in or that are old drugs that are not actually approved by FDA, or maybe introduced without benefit of the approval process. They are, in effect, the policemen for the Center for Veterinary Medicine.

The third associate directorship and thereby office is for science, and this formerly was called research. What happens here is that associate directorship is responsible for managing the Division of Veterinary Medical Research in Beltsville, which is, in effect, a farm where domestic animals are kept and research is performed for regulatory purposes. That individual is also in charge of liaison with the other FDA research facilities, the National Center for Toxicological Research in Arkansas and, also, the research labs in each of the ten regional offices of FDA; and, finally, and perhaps most importantly, for contracting out approximately $1 million worth of research a year to outside organizations, primarily universities.

Staffing levels within headquarters, the Center for Veterinary Medicine, number 253 individuals. The largest number of these are to be found in new Animal Drug Evaluation. There are slightly over a 100 there. In Surveillance and Compliance, there is slightly under 100. In the Division of Science, there are about 40 total people, between 40 and 50, depending on staffing levels. We also have our share of FDA's field resources, and the number of individuals that are in the field that are assigned to CVM activities are approximately 175. So we have a total of 428 individuals. The budget, Mr. Chairman, as you undoubtedly know, is approximately $25 million.

Mr. WEISS. What has been the history of its staffing levels and budgets over the course of the past 5 years? How do they compare today to what they were in fiscal year 1981?

Dr. CRAWFORD. The total budget has remained virtually static, if you use 1985 dollars. It has increased in total dollars by approximately $2 million over the past 5 years. And the numbers of people in the Center for Veterinary Medicine have actually increased, and that is due to the transfer of certain aspects of the Center for Food Safety and Applied Nutrition, the so-called human food safety group, to the Center for Veterinary Medicine. So approximately 40 individuals are involved in that. And if you were to look in fiscal year 1981, Mr. Chairman, you would see that the FDA's Center for Veterinary Medicine, then called the Bureau of Veterinary Medicine, had approximately 210 persons; now we have 253. It reflects this increase.

Mr. WEISS. How many new animal drugs are estimated by the Center to be on the market, which are subject to the new animal drug approval requirements of section 512 of the Food, Drug, and Cosmetic Act?

Dr. CRAWFORD. Well, we number them in the thousands. We think approximately 8,000. There are some estimates by industry officials and also by trade industry groups that there are more or less, but we would say in the neighborhood of 8,000.

Mr. WEISS. We have a document from Dr. Andrew Beaulieu, who is Director of CVM's Division of Surveillance. Isn't that correct?

Dr. CRAWFORD. That is correct.

Mr. WEISS. I understand he would have been with us except that he has an illness in the family.

Dr. CRAWFORD. His wife is having surgery today, and he is sorry he couldn't be here.

Mr. WEISS. His estimate is that there are approximately 20,000 new animal drugs on the market which are subject to the provisions of section 512.

[Dr. Beaulieu's memorandum, which was prepared for a July 12, 1984, CVM management meeting, follows:]

MONITOR MANUFACTURE, DISTRIBUTION, LABELING & USE

VMO's -1000 reviews of ads, promo. material, labeling

VMO's & Chemists -1200 advisory opinions regarding the legality of various products/practices.

CSO's -process and coordinate all this activity

Is ~~it~~ product a food, drug, device, biologic, pesticide? Is it misbranded? NAD? Approved? Interim marketing privileges?

Note significance of reviews these each is subject to ~~discharge~~ challenge in court. With current resources we can devote roughly 3.5 hrs per review/VMO, chemist n CSO. This is not enough time. ~~1000~~.

About once an hour, every hour BVM is in operation, a regulatory decision of this nature is ~~reached~~ made.

What should we do about it?

Check literature, call experts, etc.

~~Subject to challenge in court.~~

We're burning out good people and we're only scratching the surface of an industry that has been and remains largely unregulated.

1. 1000 NADAs for marketed products

   2000 products = total approved

2. Vet Labs, Lenexa, Ks 2000 labels - no approvals

3. Estimate # products/# firms

   20,000 + / 600

4. 90% of products on market unapproved.

5. GMP status largely unknown but generally considered poor.

6. FY83 compliance program
   inspect every mfr.
   collect every label
   drug listing status
   to provide a profile of the industry so we could direct our resources to where they were needed most.

Obviously recent resource restrictions have made a bad situation worse: 1.) Because our ability to regulate has, in fact, been curtailed and 2.) because industry's perception of the situation has caused violations to increase in both number and severity. Industry is finking on itself with increasing frequency. I believe this supports the previous statements. This puts BVM in a precarious position. In the past, violations might have gone unregulated because they went undetected. Industry is eliminating that excuse. If the violations go unregulated after they are reported to BVM it must mean that BVM lacks the will or ~~the where-with-all to regulate~~. Once it becomes clear to firm A that we aren't going to do anything about firm B, then it must also be safe for firm A to do the same thing. Industry is testing us and anyone who thinks the industry won't sink to the lowest level of compliance they can get away with doesn't appreciate the competitive pressures in the marketplace. [It takes far less energy to maintain a mass at a constant speed than it does to accelerate it to that same speed following a drastic deceleration.]

We need urgently a 50% increase in field and HQ resources relative to this objective. This translates to 1 clerical, 1 chemist or technician, 2 VMO's, 2 CSO's and 12 field personnel (primarily inspectors/investigators). Once industry perceives that we have lost the ability to remove unapproved competitive NAD's from the market, they will either be unwilling to invest the resources to develop or refine their own products or they will simply elect to market the products without approval until we catch them (after which they may perceive we won't do much anyway). We must improve our regulatory credibility or the whole system will break down.

We need to improve our information storage and retrieval capabilities to bring some order out of the chaos. DS, which already has the most extensive microfiche filing system in BVM, needs to expand that file to incorporate labels for every product on the market to be associatd with a regulatory decision on each to assure uniformity of regulation. The procedures to accomplish this are currently being developed. On the order of $20,000 for additional fiche storage and for fiche processing will be needed.

Computeried data processing systems are also needed to enhance reaching this goal. Two major ones involve registration and drug listing and will be discussed later. However, we also need a program to maintain an accurate inventory of firms subject to PMS 65 & to process data on GMP status of inspected firms. This is currently being maintained on an AB Dick Word Processor but the capacity of this equipment will soon be exceeded. ADP development costs for this program are estimated to be $75,000.

Within 3-5 years, BVM personnel should be in a position to rapidly (within minutes):

1. Retrieve a label for virtually any veterinary product being marketed at that time.

2. Retrieve a prior regulatory decision regarding that particular product or the class of products ~~of which it is a member.~~

3. Retrieve a compliance profile of the manufacturer including general manufacturing practices.

4. Initiate an assignment memo to the field to obtain such information and get it into the system for any new manufacturers.

It is pathetic that the purportedly greatest animal drug regulatory organization in the world doesn't even know what it is responsible for regulating. [Can you imagine Ma Bell operating without an accurate list of subscribers?]

REGISTRATION AND DRUG LISTING SYSTEM

It is obvious that Congress couldn't envision the Agency operating effectively without knowing who and what it was regulating because they made the implementation of such information gathering and processing systems mandatory under the FD&C Act. Unfortunately, the Agency has never fully implemented these requirements, ~~particularly the more recent (if 1972~~ is recent) requirements for drug listing.

About two years ago, NCDB which wasn't doing the job anyway in a manner useful to BVM, stated that it no longer considered itself responsible for monitoring animal drug listing information and handed over a partial data base and about 6000 unprocessed forms to BVM. Those forms have been processed and the data base updated but it is no more than 50% accurate even so. In the meantime, since DS did not get added resources to accomplish this function and, in fact, has suffered a 16% loss in overall resources, incoming info from the firms has backlogged to approximately 5000 forms. These have been manually edited and are in the process of being keyed-in using NCDB's online data entry system, but there is no way we can reduce the backlog and process the 200+ forms which arrive every month using the 1.5 py currently available for this task. Furthermore, the existing software is patched together by NCDB, is inefficient and undocumented and generally doesn't meet BVM's needs. Even if we had all of the information processed to the point of updating the file (which much of it already is) we have to rely on NCDB to perform that update and they've already made it abundantly clear that isn't their responsibility. Therefore, we urgently need to develop our own drug listing ADP system in accordance with our own needs. This could be accomplished for roughly $100,000. Similarly, we need to develop a veterinary firm registration ADP system to meet our own needs. Development costs for this system would be somewhat less than $100,000 particularly depending upon the status of medicated feed mills which comprise the bulk of the inventory ie, 12,000 firms. The responsibility for maintaining this inventory will shift to BVM in Jan. 1984 when a new cycle begins. Depending upon 2nd generation implementation some existing resources may be freed up to accomplish this function but they should be earmarked for this purpose now and their organizational and PMS placement decided ASAP, ie. will they remain in DAF or be shifted to the Registration Staff in DS, will they work under PMS 67 or PMS 65? It would seem that all registration functions should be under one PMS, as far as organizational location; I'm open to suggestions.

In any event, we need 2 technicians for firm registration and 3 for drug listing in order to reasonably implement our Congressional mandate and place ourselves in a position in which to effectively plan to regulate the veterinary pharmaceutical industry under PMS 65.

PROCESS INQUIRIES

While we are currently processing 400-500 of these per year and the quality of the responses are certainly adequate, we cannot respond in a timely fashion. Other than Congressionals and those received which involve a signature of a high level FDA official, we can respond only within months to most requests given current resources. It obviously creates a poor impression when a school child or a concerned consumer or a potential manufacturer writes the Agency and doesn't get a response for several months, but that's the best we can do with current resources.

Another CSO and 1/2 VMO would greatly improve our ability to meet this objective although we can continue to function in the near term with current resources.

VETERINARY DRUG EXPERIENCE

Where we are now:

4 VMO's ↑
1.5 chemists reviewing > 3000 DERs/year including > 1400 ADRs
DERs may contain new studies, literature references, promotional material, 514.8(a)(5) changes, new stability or other mfg.data, new distributors, etc.
ADRs require review of basic tox. data in NADA & literature, review of previous ADR reports, & frequently follow-up with complainant to get additional data. About 10% of DER reviews result in some sort of further action on the part of DS/BVM, ie, letters, supplement review, causal review, FR publications, etc. Given current resources we can devote about 3 hours to each DER/ADR review (That's not enough time).

Consistent 10% increase/year for last 5+ years. Several things are happening which make the situation worse.

1) NADA rewrite proposes to shift much work from review of voluntary supplements to review of DER's by eliminating the need for supplements provided some data is submitted to DER.

2) 510.300 rewrite increases data requirements of DERs.

3. As SE speeds its approval process, there is an apparent increase in the need for DS to pick-up-the pieces eg.

	Approved	Complaints	Action
Compudose	3-12-82	154/9000/48	Relabeling, reformulation
Topagen	6-18-82	8/32+/0 (8 human)	Stop mkting, recall reformulation
Mitaban	4-30-83	56/50/7	Remanufacturing, relabeling
Eqvalan	2-22-83	31/47/8 47 17	Dear Doctor letter relabeling

Furthermore the BVM effort needed to get correction once a product is approved is far greater than prior to approval (not to mention the cost to the mfr. and the consumer of recalls, remanufacturing, and animal death and debility). We don't do anyone a favor by approving an unsafe, or poorly manufactured product.

4. In general, the industry has become more contentious as they have perceived either our will or our ability to regulate to decrease. It will take significant effort to reverse this trend.

5. Because of the generally increased sophistication of the industry (at least that portion that holds approved NADAs), the rigor of our reviews has had to increase. An obvious point of contention is whether reported adverse effects are actually related to a particular product. We have already initiated an algorithm to provide consistency and objectivity to ADR review. This will need some refinement based on actual experience. One of the principle requirements of the algorithm is an accurate assessment of the new ADR relative to all previous reports. This requires the ability to update and retrieve the ADR profile of each approved product quickly and efficiently. An ADP system is absolutely essential to this function. Development costs for such a system are estimated to be $150-200,000 with possibly significant annual operating costs in the future depending upon the type of system developed.

Additional ADP needs involve a refined (or redeveloped) and updated NADA index ($200,000), a refined (or redeveloped) and updated DER index ($75,000) and a product defect file (similar in intent to the ADR history file). ($30,000).

[illegible]

Within 2 years VMO's or chemists should be able to generate up-to-date printouts of NADA, DER, ADR or product defect histories or obtain these on-line at a central terminal, within minutes to hours, in 3-5 years they should be able to do this from their desks within minutes.

While increased use of newer technologies will permit us to meet an acceptable standard in our review of current levels of information regarding DERs and adverse drug experience, a number of other factors already mentioned will cause an increase in the number of DER and ADR submissions. Furthermore it is our responsibility to develop new methodologies to improve our ability to monitor ADRs. Therefore, additional HQ personnel in the form of 1 technician, 1 chemist and 1 VMO are needed in the near term with a similar additional increase within 5 years.

CAUSAL REVIEW

A great deal depends upon BVM maintaining a viable causal review program. With current resources we can devote no more than 1 py to this objective and that must be at the expense of lowered quality in other objectives. We have already given a great deal away in terms of regulation (the supplemental approval policy) and are proposing an additional sweeping change in policy (generic approval) based exclusively on our ability to identify and correct problems in marketed drugs and update data to current standards where such problems exist, ie. to perform causal reviews. 1 py would probably not be interpreted as a serious effort by any outside investigating body. Each such review is extremely complex and time consuming and is virtually certain to be challenged if findings are adverse to industry. Therfore they must be rigorously and scrupulously performed and are very resource intensive.

We need, in the near term, 1 additional VMO to work toward this objective and in the longer term (3-5 years) at least 1 more VMO.

VOLUNTARY COMPLIANCE

Rx labeling guide - industry
Dispensed Rx drug labeling guide - practitioner
Annual or ~~semi~~ semi-annual ADR report
ID of approved new animal drugs.

Dr. **Crawford**. As I said, there are varying estimates. And within the Center, there are those that believe the 8,000 figure is too conservative, and Dr. Beaulieu is one of those. He says in the worst case situation, I believe, that there could be as many as 20,000. And I do not disagree with that.

Mr. **Weiss**. Approximately how many of these 20,000 drugs have been approved for marketing by FDA?

Dr. **Crawford**. Well, we do not have exact figures on that. But there is—there are various estimates by Dr. Beaulieu's staff that these are perhaps a majority of animal drugs being used—and this, please understand, would consider many small products with low volumes that are actually not of very much use. But if you consider all of them, I believe that Dr. Beaulieu's staff firmly believes that the majority are not the subject of an NADA.

Mr. **Weiss**. What do you mean, are not the subject of—

Dr. **Crawford**. In other words, they are not officially approved by FDA.

Mr. **Weiss**. Well, as a matter of fact, Dr. Beaulieu's estimate is that of the approximately 20,000 animals which he says are subject to NADA approval requirements, only about 2,000 have, in fact, been approved for marketing by FDA. Do you have any reason to disagree with that estimate?

Dr. **Crawford**. No. I don't disagree with it on the face of it. Those are estimates, I believe, and the figure could be the 90 percent or it could be slightly less. I don't think anyone, though, disagrees that the majority are not approved.

Mr. **Weiss**. But again, Dr. Beaulieu is the Director of CVM's Division of Surveillance and Compliance. Isn't that right?

Dr. **Crawford**. Yes.

Mr. **Weiss**. So he would be in as good a position as anyone in the agency to know about this, wouldn't he?

Dr. **Crawford**. That is true.

Mr. **Weiss**. Does this mean that as many as approximately some 18,000 or 90 percent of the new animal drugs in use are being marketed in violation of the premarket approval requirements of the law?

Dr. **Crawford**. Yes.

Mr. **Weiss**. Now, Dr. Beaulieu has also written that "many of these [unapproved] products are intended for, or are being diverted to, use in food-producing animals," which could "create health hazards * * * for humans consuming residues in food from animals improperly treated."

[Excerpts from a document written by Dr. Beaulieu in early 1984, as well as an April 5, 1984, memorandum containing materials including one of these quoted statements, follow:]

MONITORING MARKETED ANIMAL DRUGS AND DEVICES

- THE MAJORITY OF ANIMAL DRUGS CURRENTLY BEING MARKETED ARE NOT THE SUBJECT OF NADA APPROVAL.
- UNDER CURRENT STANDARDS, VIRTUALLY ALL ANIMAL DRUGS ARE NEW ANIMAL DRUGS.
- A MAJORITY OF CURRENTLY MARKETED ANIMAL DRUGS ARE IN VIOLATION OF THE FD&C ACT.
- MANY OF THESE PRODUCTS ARE INTENDED FOR, OR ARE BEING DIVERTED TO, USE IN FOOD-PRODUCING ANIMALS.
- FAILURE TO REGULATE THESE PRODUCTS AFFECTS THE HEALTH OF MAN AND OTHER ANIMALS.
- SINCE THIS REGULATORY TASK FAR EXCEEDS CURRENT RESOURCES, REGULATORY PRIORITIES SHOULD BE ESTABLISHED, WITHOUT ALERTING THE REGULATED INDUSTRY, IF POSSIBLE.

DEPARTMENT OF HEALTH & HUMAN SERVICES

[illegible]

Memorandum

Date APR 5 1984

From Director, Center for Veterinary Medicine

Subject Strategic Planning Go-Away

To See Addressees

Your participation in the planning process this year certainly contributed to the success of our recent presentation to Dr. Novitch on our FY 86 Budget. We now need to "press on" and look a little deeper into our mission and how we achieve our objectives using different assumptions.

Staff ✕ We will once again have a two day go-away (site to be determined) during the month of June. The agenda for the first day will be a continuation of the process initiated at the Harpers Ferry conference last year. The Associate Directors and/or PMS managers should plan to make a presentation lasting 20-30 minutes. The difference this year is that these presentations will address one or more of the CVM goals established during last year's planning process (Attachment A). Consideration should be given to reinforcing existing objectives, adding new objectives or suggesting rationale for the deletion of some.✕Should there be a perceived need to generate new goals or to substantially modify the existing goals, please submit these changes to Carol Gray's office by May 18, 1984. This is necessary so that the new information can be disseminated and each Associate/PMS manager can be prepared to address his portion of the new goal.

The second day will be devoted largely to exploring more effective and efficient ways to conduct our programs. Despite the current trend toward containing federal expenditures, the American public continues to expect greater protection against health hazards. The different set of assumptions for the second day discussions revolve around the current trend of 5-10 percent annual reductions in personnel ceilings. I believe that the demands for continued vigilance to ensure safe and effective animal drugs and human food safety can be met even under this condition. This environment will demand thorough planning, innovative resource management, well designed and conducted research projects and a clear vision of what we must accomplish.

This is our challenge as managers. All of us must take every opporutunity to use the best management principles in reevaluating our basic functions and how we perform them.

What we will do is "invent" the future of CVM. The emphasis will be on defining what we must do and do well as opposed to what we could do. Then we need to look very closely at how we can achieve our mandatory functions plus the important supporting tasks using various mixes of regular employees, consultants, contracts and other available resources. A conceptual outline of how to approach this task is Attachment B. We will have some discussions of this process in the next few weeks to insure we are headed in the same direction. A recent article on strategic planning is attached to provide food for thought ~~(Attachment C)~~.

I look forward to working with all of you in this effort, and I am sure that this year's program will be even more productive than last year's.

Lester M Crawford

Lester M. Crawford, DVM, PhD

Attachments

Addressees:

Dr. Carnevale (HFV-100)
Dr. Bixler (HFV-200)
Dr. Norcross (HFV-300)
Dr. Crandall (HFV-400)
Dr. Teske (HFV-500)

cc: Dr. Guest (HFV-2)
Mr. Nichol (HFV-10)

I. TO MORE EFFECTIVELY MONITOR THE MANUFACTURE, DISTRIBUTION, LABELING AND USE OF VETERINARY DRUGS AND DEVICES THEREBY REDUCING ILLEGAL VETERINARY DRUG DISTRIBUTION AND USE.

To more efficiently monitor the manufacture, distribution, labeling and use of veterinary drugs and devices, thereby reducing illegal veterinary drug distribution and use.

The major portion of the mission of the Bureau of Veterinary Medicine is to ensure the safety of animal-derived human food products and the safety and effectiveness of drugs for use in animals. To this end, the Bureau has been attempting to monitor the manufacture, distribution, labeling and use of veterinary drugs and devices, and to safeguard against the illegal manufacture, distribution, and use of veterinary drugs. The illegal manufacture, distribution and use of veterinary drugs in the United States have reached alarming proportions. Such unauthorized practices create health hazards for animals ~~mistreated with the drugs and for~~ humans consuming residues in food from animals improperly treated. Of particular concern are the extralabel uses of drugs in food-producing animals, the use of unapproved drug combinations, and the flagrant disregard for the regulations governing the manufacture and distribution of veterinary products.

During the period from 1984 through 1988, the Bureau plans to:

1. Continue current surveillance and compliance activities supported by established compliance program requirements and regulatory action by inspections, reports of over-tolerance, causal reviews, etc.

2. Increase resources devoted to Drug Listing and Drug Registration to bring this established program up to date to create and maintain an accurate and current inventory of firms and products. In order to support increasingly complex and sophisticated regulatory actions and industry clinical practices, major new data processing systems will need to be developed.

3. Develop (in cooperation with the voluntary compliance effort) a data base to determine the extent of illegal manufacture, distribution, and use of veterinary drug products.

4. Increase resources devoted to monitoring recently approved animal drugs to provide additional oversight on the increasing number of approved drugs resulting from the accelerated review process.

5. Prepare for major additional workloads predicted if the FOI pre-release notification rules are adopted and/or if the Generic Drug Policy and NADA rewrite are implemented.

6. Implement a cooperative effort with FSIS/USDA on a program to monitor meat for residues of recently approved drugs in food-producing animals.

In an effort to reduce illegal veterinary drug manufacture, distribution and use, the Bureau intends to accomplish the following:

1. Identify and quantify the scope and magnitude of various compliance problems, including clinical investigator and foreign inspections so that compliance activities can be directed toward the most significant violations.

2. Develop data systems to facilitate compliance activities and illuminate possible broad solutions to problems in the ensuing years.

3. Develop voluntary compliance programs which create an awareness of the problem and the potential human and animal health hazards it presents.

4. Provide opportunities for discussion/exchange of ideas on the problem and possible solutions with members of the veterinary and agribusiness communities.

5. Conduct research to define and characterize the significance of various compliance problems and provide data to support the development of both voluntary and regulatory compliance programs.

6. Develop an improved field compliance guide on residues in order to have credible, effective, cooperative USDA/Bureau/District effort with the goal of (in conjunction with the voluntary compliance effort) reducing the incidence of over-tolerance residues in animals slaughtered for human food.

It is estimated that the current scope and scale of illegal veterinary drug manufacture, distribution and use in the United States is of such magnitude as to encompass the entire agribusiness community--drug manufacturers, drug distributors, livestock producers and, also veterinary health professionals and practitioners.

Relative to the current status of the animal pharmaceutical and premix manufacturing and distribution industry (an industry with sales of over 1 billion dollars annually), it is estimated that 80-90% of products currently marketed are not in compliance with the FD&C Act, with perhaps 10-20% being significantly out of compliance (i.e. with potentially significant adverse effects on animals or humans). The routine availability of unapproved (and frequently completely untested) animal drug products has a widespread detrimental effect on the multibillion dollar animal production industry. The intense promotion of unapproved products within the highly competitive animal production industry results in a general increase in non-compliance due to perceived economic advantages associated with drug misuse. This growing problem of non-compliance must be checked quickly before the Agency loses all credibility with the industry and the general public.

Because of the perceived magnitude of the problem, there is a definite need to more clearly qualify and quantify its scope through the establishment of a valid data base. And precisely because the problem does appear to cross all agribusiness/animal health spheres of influence and interest, the development of a significant part of such a data base--in order to be unbiased and statistically valid--would likely require that a survey be undertaken by an entity outside the spheres of these tested interests, preferably through a private sector contractor experienced in surveys and underwritten by FDA/BVM.

BVM has planned the following activities for FY 84, 85, and 86 specifically to reduce illegal veterinary drug manufacture, distribution and use.

For FY 84, BVM proposes to work with the various segments of the animal health industry to clarify and possibly quantify some parts of the problem (i.e., establish a portion of the data base); we will work with/through the American Veterinary Medical Association to adopt a supportive position on proper labeling for prescription drugs; finalize and adopt a BVM position directed to practitioners on proper drug labeling; maintain existing and new compliance programs designed to identify and quantify the extent and significance of non-compliance associated with the manufacture and distribution of animal drugs; and develop data processing procedures to expedite this evaluation. Under the umbrella of the voluntary compliance program, BVM staff will prepare/present speeches for practitioner researcher, drug distributor, and producer organizations and participate in national/state veterinary association meetings; prepare/edit articles for trade and industry publications and for the FDA VETERINARIAN; develop informational/educational materials (e.g., BVM Memos, brochures) on proper labeling of drugs and extralabel use of drugs; publish a list of approved animal drugs; and develop/make available a prescription labeling guide.

For FY 85, the Bureau plans to continue the FY 84 programs on a maintenance level. Projected plans include conducting seminars at veterinary schools on the illegal use of drugs' problem, developing a slide/tape show for use with national/state veterinary associations, developing a program to encourage drug manufacturers to "advertise" FDA approval on their products, collecting data on the progress of the campaign against illegal use of veterinary drugs (i.e., followup survey).

For FY 86, BVM will continue the previous programs on a maintenance level; project plans include producing print and radio public service announcements and preparing and distributing adverse reaction reports.

Resources Required:

FY-84	FY-85	FY-86	FY-87	FY-88
-	12 FTE HQ	2 FTE HQ	8 FTE HQ	-
$500,00	16 FTE Fld	$26,000	-	-

2. TO ENHANCE THE SCIENTIFIC CAPACITY OF THE BUREAU TO IDENTIFY NEW TECHNOLOGIES AND RESOLVE STATE-OF-THE-ART ISSUES IN VETERINARY MEDICINE AND MORE EFFECTIVELY CONDUCT SCIENTIFIC AND ADMINISTRATIVE REVIEWS OF ANIMAL DRUG AND FOOD ADDITIVE APPLICATIONS. THIS WILL INCLUDE HEARINGS ON ANTIBIOTICS IN ANIMAL FEED AND ON AGENCY PROPOSALS TO WITHDRAW APPROVAL OF SEVERAL NADAs WHOSE CONDITIONS OF USE ARE NOW RECOGNIZED AS PRESENTING POTENTIAL RISKS TO CONSUMERS.

To enhance the scientific capacity of the Bureau to identify new technologies and resolve state-of-the-art issues in veterinary medicine and more effectively conduct scientific and administrative reviews of animal drugs and food additive applications.

The primary function of the Bureau is to regulate the interstate marketing and use of veterinary drugs, feeds, food additives, and approving only those products shown by scientific data to be:

1. safe and effective for their intended uses;
2. safe for consumers of food products derived from animals;
3. safe for the environment (e.g. carcass/waste disposal).

Also, the Bureau monitors the performance of these products to assure that they remain safe and effective for their intended purposes. An essential prerequisite is the establishment of a strong scientific base grounded in sound scientific research activities designed to provide both scientific data and special knowledge, skills, and expertise as required to support policymaking, regulatory decision making and implementation, and voluntary compliance initiatives.

Research is one of the critical resources employed by the Bureau to achieve its mission of assuring the safety and efficacy of animal drugs and food additives. It must be relevant, of the highest quality, and must be completed in a timely manner. Primary objectives of the research program include:

1. Development of scientific data contributing to greater understanding and efficiency in the interpretation of toxicity and efficacy data and development of improved methods of safety (both human and animal).
2. Conducts research in support of minor species programs.
3. Development of analytical methods for detection, identification, and quantitation of drugs and other chemicals present in animal feeds and in food derived from animals.
4. Investigation of the myriad interacting factors that contribute to alterations in responses to animal drugs, food additives, and other xenobiotics.

Beginning in FY-84, the Bureau proposes new research initiatives in pharmacology and pharmacokinetics and in biotechnology and genetic engineering and bacterial genetics.

Pharmacology and Pharmacokinetics

Currently the Bureau has, or is developing, a number of policies, guidelines, and procedures that rely on, relate to, or involve pharmacokinetic principles, i.e.:

✓ 1. Minor use/minor species policy

2. Combination drug policy

3. Dose determination procedures

4. Bioequivalency guidelines

5. Human Food Safety policy

The Bureau's immediate need for advance expertise in pharmacokinetics is considered to be critical. Specifically the need is for a program to define and demonstrate applications of pharmacokinetics principles in the regulatory process. The objective of the program is to identify deficiencies in the science base required to relate pharmacokinetic principles and modeling to regulatory processes and to initiate research planning strategies not only addressing those deficiences but creating research and test capability designed to provide the necessary long-range science base required to support regulatory activities.

Biotechnology and Genetic Engineering

The Bureau must develop a scientific data and information base related to the regulation of biotechnology-derived feedstuffs, drugs/devices, and biologics. The program should be designed to:

1. Define and characterize the current state-of-the-art and forecast significant developments and breakthroughs anticipated during the next ten years;

2. Develop information resources and training programs for target constituencies (Bureau and Agency personnel, industry, etc.);

3. Define and characterize regulatory implications that are unique to products derived from the new biotechnology and initiate planning strategies to address those regulatory implications;

4. Define and characterize the basic science requirements imposed by this technology, including scientific knowledge and expertise as well as capabilities, both scientific research and testing, that will be required in order for the Bureau and the Agency to effectively regulate biotechnology products.

Bacterial genetics

The Bureau must enhance its expertise with regard to the issue of drug induced bacterial resistance transfer. The proposed regulatory action (21 CFR 558.15) on low level use of antibacterials in animal feeds has been an ongoing project for many years. Contract studies commissioned several years ago are nearing completion and the data being readied for analysis. A priority effort by the Bureau on 558.15 must be established through 1986 encompassing the following objectives:

1. Continue to monitor and collect data from ongoing contracts such as Seattle King County.

2. Formulate our strategy on scientific questions that need to be answered to resolve resistance issues.

3. Review of data from contracts through consultants.

4. Improve expertise through acquisition of a bacterial geneticist.

5. Respond to Hearing and Congressional oversight on the issue.

The improvement of the Bureau's expertise in the areas of pharmacology, toxicology and pharmacokinetics and RDNA technology will facilitate reviews of FAPs, INADs and NADAs. This improved expertise can be accomplished by specialized recruitment strategies and by long-term training assignments. Decreasing the amount of time it takes to review an application requires both increasing staff resources and lessening the requirements on submission from industry. During the period from 1984 through 1988, the Bureau plans to:

1. Continue to strengthen the expedited review program and to expand it beyond the area of therapeutic agents to include production drugs and food additives.

2. Bring about, in FY-85, a generic drug policy to allow for duplicates of post-1962 products. The proposal for this policy is expected to be published in the Federal Register in FY-84.

3. Design better research in order to help reduce review time.

4. Identify more efficient ways of reviewing applications through continuing program analysis and evaluation; i.e., OPE's recent evaluation of the office of Scientific Evaluation's procedures for reviewing NADAs and INADAs. One of the findings of this OPE study identified the need for better communication with industry. In response to this finding and as part of the Bureau's voluntary compliance program the following activities are planned:

   a. Workshops are planned with industry in order to convey information which will help correct manufacturing deficiencies. The Office of Scientific Evaluation will conduct the workshops; the Office of Voluntary Compliance and Operations will coordinate and provide administrative and educational support and improve EIR handling.

   b. A Question and Answer booklet is planned for industry, informing sponsors of the requirements for getting a drug.

5. Publish notices of opportunity for hearings, and if indicated, hold hearings on proposals to withdraw approval of several animal drugs for which new information, not available at the time of approval, raise serious concerns about the human food safety of their approved conditions of use.

Resources Required:

Pharmacology and Pharmacokinetics

FY-84	FY-85	FY-86	FY-87	FY-88
5 FTE's	3 FTE's	-	-	-
$100,000	$150,000	$150,000	$150,000	$150,000

Biotechnology and Genetic Engineering

FY-84	FY-85	FY-86	FY-87	FY-88
2 FTE	2 FTE	-	-	-
-	$250,000	$500,000	$250,000	$250,000

Bacterial Genetics

FY-84	FY-85	FY-86	FY-87	FY-88
2 FTE	1 FTE	1 FTE	-	-
$90,000	$60,000	$40,000	-	-

Scientific and Administrative Reviews of EIRs, INADs, NADAs and FAPs

FY-84	FY-85	FY-86	FY-87	FY-88
1 FTE	2 FTE	7 FTE	4 FTE	7 FTE
Resources:				
$170,000	$200,000	$200,000	$200,000	$200,000
Equipment:				
$ 50,000	$ 80,000	$ 60,000	-	-

3. TO ESTABLISH PROCEDURES FOR MORE EFFECTIVELY EVALUATING ADVERSE DRUG EXPERIENCES FROM MARKETED VETERINARY DRUGS AND DEVICES.

This major objective of the Bureau is to more effectively evaluate adverse drug experiences from marketed veterinary drugs and devices.

The review of an Adverse Drug Reaction (ADR) includes a review of basic study data included in the NADAs, a review of the pertinent literature, review of previous ADR reports, and frequently a follow-up with the complainant to obtain additional information. The ADR reports on file in BVM are a source of data. However, these data must be extracted from the files and analyzed. This requires the use of epidemiological and statistical expertise and methods, as well as more sophisticated ADP capabilities to manage the increasing amounts of data. In FY-82 the Bureau reviewed 3000 Drug Experience Reports (DERs) and 1400 ADRs. There has been a relatively consistent 10% increase in such reviews over the last four to five years. Any increase in NADA approvals results in an increase in DER submissions at a rate of about 2.5 DERs/NADA. DERs contain new studies, promotional materials, labeling and ADRs. Approximately 10% of DER reviews result in further action, some of which may be very resource intensive.

Clearly, an increase in DER and ADR reviews creates a significant derivative workload. With the use of ADP systems, the DER and ADR review process can be expedited. A primary result of an adequate ADP system would be the generation of several standard reports which would, at a glance, give an overview of the available information by drug class or specific drug. Similarly, VMOs/reviewers would potentially be able to more quickly spot trends or patterns in the data reviewed. A vital component in such an ADP system would enable certain statistical testing of data to accommodate epidemiological analyses. Consequently, BVM would have a better potential for arriving at concrete regulatory decisions based on appropriate scientific methods of data analysis.

By fiscal year 1986, the NADA rewrite should shift much work from review of voluntary supplements to review of DERs. Significant increases in efficiency of DER and ADR reviews have already been implemented, but further advances can be made in the area of automated data processing. Within two years VMOs or Chemists should be able to generate up-to-date printouts of NADAs, DERs, as well as ADR and product defect profiles. They should be able to obtain these on line from a central terminal within minutes to hours; in three to five years they should be able to do so from their desks in minutes.

Much that is learned about an animal drug's safety and effectiveness is derived from surveillance methods applied after the drug is marketed. As the use of a drug product increases to involve thousands of animals, there is an increased likelihood that adverse drug experiences will occur and be reported. However, no single, mega-surveillance system can adequately monitor these marketed drugs. The Bureau needs and utilizes several monitoring systems, each designed to accomplish a specific aspect of the entire surveillance effort. There is a continuing need for BVM to refine its surveillance methods as well as to implement appropriate new ones. This is especially important as the Agency now utilizes expedited reviews of drug applications (i.e., expedited review approvals). The DER is also multi-faceted, with some DERs requiring more immediate and/or in-depth review than others. BVM must be able to identify and prioritize these types of reports.

During the period from 1984 through 1988, the Bureau plans to:

1. Refine procedures for identifying and characterizing DERs which warrant immediate correction of labeling, formulation, manufacturing procedures, or causal review.
2. Update existing methods of information collection by revising 21 CFR 510.300, reorienting the Veterinary Drug Experience Reporting Program (VDERP), promoting direct submission of ADR cards, and developing new data gathering methodologies, e.g., telephone survey.
3. Create automated data processing (ADP) capability for all veterinary drug adverse experience reports.
4. Enhance, through training, transfers, sabbaticals, new hires, etc., the epidemiological expertise of the Division of Surveillance.

However, even such increases in efficiency will not be sufficient to overcome the increased workload. Additional personnel and monies will be needed.

Resources Required

FY 84	FY-85	FY-86	FY-87	FY-88
-	5 FTE HQ	5 FTE HQ	-	-
$200,000	-	-	-	-

4. TO INCREASE COMPLIANCE WITH THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BY THE REGULATED INDUSTRY THROUGH THE USE OF VOLUNTARY COMPLIANCE ACTIVITIES.

To educate and inform regulated industry through voluntary compliance programs to understand their responsibilities under the Federal Food, Drug, and Cosmetic Act; and to fully participate in the coordination and exchange of international veterinary product issues.

The goal of the voluntary compliance program is to conduct broad nationwide information/educational programs designed to increase compliance with the Federal Food Drug and Cosmetic Act by the regulatory industry. This effort is primarily directed towards increasing firms understanding of their responsibilities under the Act and encouraging acceptance and participation in self-inspection and other quality assurance programs. These programs ~~will help to insure the safety and~~ effectiveness of animal feeds and drugs administered to food-producing animals intended for human consumption. To carry out the Voluntary Compliance during the period FY 84-88, BVM staff will:

1. Attempt to reduce the illegal distribution, sale and use of veterinary drugs, especially for use in food producing animals, through publishing FDA Veterinarian articles, educational printed materials for practitioners, distributors, and producers, and developing speeches for BVM speakers to deliver to national organizations.

2. Provide information and guidance to practitioners and researchers on the proper labeling of drugs dispensed for animal use.

3. Coordinate cooperative programs for national and state veterinary associations and conduct seminars at veterinary schools and universities.

4. Attempt to reduce the incidence of violative residues in animal feeds and animal-derived human foods through disseminating educational printed materials to feed manufacturers, suppliers, and animal producers; supporting USDA with the Residue Avoidance Program; delivering speeches at industry meetings; and conducting contamination and residue prevention seminars for industry.

5. Raise the awareness among regulatory officials in government, the regulated industry, and the general public of BVM's responsibilities for protecting the public health by coordinating the small business programs and consumer affairs program. This objective will require all the previously mentioned activities such as providing industry, veterinarians and consumers with educational materials, delivering speeches, conducting seminars and expanding FDA Veterinarian content and distribution.

6. Promote implementation of the recommendations of the Second Generation Medicated Feed Task Force through education of practitioners, feed manufacturers, and animal producers.

7. Publish a list of approved animal drugs.

8. Attempt to reduce salmonella contamination of feeds and animal-derived human foods through speeches at industry meetings and workshops to develop industry guidelines for salmonella contamination prevention, and FDA Veterinarian articles.

9. Develop a slide/tape show for use with national/State veterinary associations.

10. Develop a program to encourage drug manufacturers to "advertise" FDA approval of their products.

11. Develop plans to produce public service announcements for both print and electronic media.

12. Prepare and distribute adverse drug reaction reports.

13. Conduct research to define and characterize scientific aspects of Voluntary Compliance issues and to provide data to serve as the scientific basis for and content of various Voluntary Compliance programs.

14. Plan and coordinate two international meetings on voluntary product issues.

15. Coordinate BVM activities in support of development of an international compendium of veterinary drugs.

16. Coordinate the international distribution of data, regulations, guidelines, etc., developed by BVM.

Resources Requires

FTE's Headquarters

FY-84	FY-85	FY-86	FY-87	FY-88
7.6	2.0	3.0	-	-
$125,000	$230,000	$312,000	$331,000	$318,000

5. TO IMPROVE THE BUREAU'S SCIENTIFIC BASE FOR RENDERING SOUND REGULATORY DECISIONS ON ANIMAL FEED CONTAMINANTS.

The introduction of industrial chemicals and pesticides into the animal feed supplies and the use of mycotoxin-containing feed ingredients represent areas of great concern. Contamination may result from a variety of ways, including the misuse of chemicals, industrial accidents, improper disposal of industrial chemicals and natural means. The use of contaminated animal feeds has resulted in economic losses to livestock producers, feed manufacturers, and processors of food animals and their food products. Also, a hazard to human health may result from the deposition of these contaminants in meat, eggs, and dairy products.

The Bureau has dealt with feed contaminants over the years using traditional tools such as surveillance and research. There does not appear to be any reason to interject major changes at this time. However, in light of dwindling resources coupled with increasing demands for a purer (i.e., safer) food/feed supply, modification of these activities are needed, primarily in the surveillance area.

For each of the last three years, the Bureau's feed contamination compliance programs (chemical contaminants and mycotoxins) have analyzed roughly 1000 samples. Even if all these samples were random, which they are not, this sampling size is grossly inadequate for making inferences about the safety of the nation's feed supply. Likewise, and probably more important it is difficult to use this information for mapping trends. In FY-83, the Agency provided the Association of American Feed Control Officials (AAFCO) seed money to initiate a national feed residue data bank hopefully storing data not only generated by the States but from Federal agencies and the private sector as well. This information will give us a much broader and in some cases, a more in-depth picture for purposes of directing our compliance programs and for giving guidance for future research. This effort is important since we have been critized by Congress on several occasions that our contamination programs are too weak. Therefore, we intend to actively pursue a successful AAFCO Feed Residue Data Bank with both money and people which ever is needed.

The Office of Planning and Evaluation is presently conducting an evaluation of the Bureau's chemical contaminants and mycotoxin compliance programs. It is anticipated that this evaluation will provide insight into making the programs both more meaningful and efficient. Regardless, the Bureau does not at this time have the necesary field resources assigned to it to cover the "known" problems. For the years FY 80 - FY 83, these programs have utilized more field resources than were planned. Additional field resources are also needed to provide a higher level of coverage, something which is desperately needed. We have expanded the surveillance of animal feeds for contaminants through State contracts. In FY-83, approximately $180,000 was awarded among 10 States for analysis of animal products and by-products intended for feed use. It is our intention to continue this program, possibly obtaining additional funds.

The Bureau also needs additional personnel with toxicology training for purpose of evaluating residue data and making recommendations on regulatory actions. Improvement in the Bureau's research of chemical and biological contaminants will assist the Agency in dealing with regulatory issues, some of which have been very sensitive such as the 1983 aflatoxin in corn problems. The following activities are planned during the period FY 84 through FY 88:

1. Develop a mycotoxin research program to cover both intramural and extramural activities. Initially, prinicipal emphasis will be on aflatoxins.

Attachment B

Questions to Evaluate Your Operation

1. What must my organization do to fulfill statutory and CFR requirements?

   a. How do we do those functions now?
      - How many FTEs?
      - How many contract dollars?
      - How many interagency agreements?

   b. How could we accomplish the same work using a different mix of resources?
      - Fewer FTEs
      - More contracts
      - More interagency agreements
      - Other innovations

2. What functions have we been doing that directly support our must list but are themselves not essential to statutory or regulatory requirements?

   a. How do we do those functions now?
      - How many FTEs?
      - How many contract dollars?
      - How many interagency agreements?

   b. How could we accomplish the same work using a different mix of resources?
      - Fewer FTEs
      - More contracts
      - More interagency agreements
      - Other innovations

3. What functions are we doing now that are operating at less than a "critical mass" to achieve meaningful and timely support?

   a. How do we do those functions now?
      - How many FTEs?
      - How many contract dollars?
      - How many interagency agreements?

   b. How could we accomplish the same work using a different mix of resources?
      - Fewer FTEs
      - More contracts
      - More interagency agreements
      - Other innovations

4. What functions could be considered immediately for analysis of alternatives? What should be considered for the next 5 years?

Mr. WEISS. How many of the approximately 18,000 unapproved new animal drugs being marketed, in your judgment, present potential human food safety concerns?

Dr. CRAWFORD. Well, I do not know that I could give you a precise figure. Actually, any of them, though, Mr. Chairman, that are used in food-producing animals need to be reviewed by FDA. And we are, as you perhaps know, trying very hard to keep up with the tide of these drugs and are performing a number of strategies in order to deal with them. Some of them are manufactured in the United States and some are not, and we attempt on a continuing basis to assess where they are coming from, what they are here for, and if they are being used in food-producing animals, which would make them the highest priority. So any of them that are used in food-producing animals should be reviewed by FDA, to answer your question.

Mr. WEISS. We are trying to establish the extent of the problem, and I have an April 5 memorandum containing materials from Dr. Beaulieu in which he estimates that perhaps 10 to 20 percent of the new animal drugs on the market—or 2,000 to 4,000 drugs—are "significantly out of compliance, i.e., with potentially significant adverse effects on animals or humans." You have no reason to disagree with that estimate, do you?

Dr. CRAWFORD. No; I do not.

[The memorandum referred to, and the materials it encloses, are in the record.]

Mr. WEISS. Can FDA identify, with any reasonable accuracy, which unapproved new drugs are being administered to food-producing animals for which no other drugs of their chemical type have been approved?

Dr. CRAWFORD. Well, I think in that case we again could not give you a precise figure. Our field forces, though, in investigations of animal drug distribution houses and also investigations of on-the-farm use and dealing with veterinary medical associations and trade industry groups are charged and do regularly assess whic drugs are being used. If it comes to our attention that an unapproved drug is being used and if it has not been approved for an purpose at all, then we single it out for action. And we have over the past several years taken a number of those actions. But to giv you a precise figure at this point, I could not. In fact, we are no doing a survey of that sort of thing, and we will make availab when it is available, our best estimate.

[The information requested follows:]

There is no "system" which permits this identification. For products marketed with claims for use in food animals, several drugs or classes of drugs appear to meet these criteria:

- a EDDI (ethylenediamine dihydroidide)
- b. Neomycin
- c. Teat dips
- d. Methylene blue
- e. Vitamin/mineral preparations
- f. Some topical germicidal (non-antibiotic) products

Mr. Weiss. But right now, you do not have——

Dr. Crawford. I cannot give you that at the present time.

Mr. Weiss. It is my understanding that USDA routinely monito for residues of animal drugs only in species for which those dru have been approved. Since FDA cannot identify which unapprov new drugs are being given to food-producing animals, what was th basis of your assurance, Dr. Crawford, to a food editors' conferen on June 28 of this year that a residue violation rate of virtual zero is close at hand?

Dr. Crawford. Well, the reason for that is that—let me corre one thing. And that is, USDA does on its own volition and also i communication with FDA, from time to time, assess the presen of drugs that are not approved. For instance, the USDA has sever times in recent history looked for the drug DES, which hasn't bee approved since 1979. They also have looked for the drug chloramphenicol and several others.

Now, the difficulty in this, as you correctly point out, is that w the drug is not approved, particularly if it is not approved for an thing in this country, then we probably do not have an analytic method to look for it. And that is why we are concerned about ill gal drug uses and that is why we have attempted to correct th problem over the past several years.

Getting back more directly to your question, the statement at th food editors' conference was given in an international contex There are many countries in the world that do not have resid analysis programs and, therefore, they would be in a poor positio to know what the level of contamination of their food is. And w know of no country that expends the effort in terms of resourc that the United States does in dealing with this problem. Thos ountries that do attempt to assess residues, almost without excep-on, report a higher residue violation rate than the United States.

Then, finally, with respect to that specific question, our residue ates since 1978 have been steadily declining. They have gone rom—for instance, with the sulfa drugs, from a level which was lmost 20 percent down to a level which most of the past 5 years as been less than 5 percent. The sulfa drugs, particularly sulfa-ethazine, gives us more trouble than any other drug that we have o look for in meat, milk, and eggs. And I also pointed out in that ddress in Dallas that if we did not have that problem, we would ave a virtual zero residue rate some months of the year.

Mr. Weiss. If you did not have what problem?

Dr. Crawford. Sulfamethazine, as a residue problem. If you took way that one drug, we would not have nearly the residue problem hat we have today.

Mr. Weiss. But how could you assure a virtual zero violation ate, since USDA only monitors routinely for residues of animal rugs in species for which they have been approved, and there s no way of knowing what other uses are being made of some of hese drugs?

Dr. Crawford. Well, that is correct. They do not routinely look or them. If we have reason to suspect them, though, we work out rrangements with USDA where they would look for them. For in-tance, in 1982, when we had a DES problem in veal calves, we worked with USDA so they could analyze for that product not only n veal calves, but in other species. Chloramphenicol is only ap-roved for use in dogs and cats. We had reason to believe it was eing used in food-producing animals, so we worked out an ar-angement with USDA, really at their behest as well as with us, to ook for the product in unapproved species.

Mr. Weiss. Would you not agree that the projection that a resi-ue violation rate of virtually zero is achievable within 2 to 5 years s overly optimistic?

Dr. Crawford. It is optimistic, but it is our job to try to bring it bout, also. So we have to try to do that.

Mr. Weiss. Trying is one thing, but giving false assurances, I hink, could create problems of its own, don't you think?

Dr. Crawford. If it was a false assurance, —I hope that it is not. We have been encouraged by the recent progress, though, because hings have gotten better in the residue picture.

Mr. Weiss. Do you know what has been the reaction of those in he veterinary drug industry who are legitimately trying to comply with the law when faced with an epidemic of illegal drug sales?

Dr. Crawford. I am sorry, Mr. Chairman; would you restate hat?

Mr. Weiss. Would you agree that there is a great deal of illegal ale of veterinary drugs in the marketplace?

Dr. Crawford. Yes. I would agree.

Mr. Weiss. And my understanding is that, for whatever reason, your agency does not regularly pursue regulatory action against hose illegal drug sales.

Dr. Crawford. No. I would not agree with that. We do pursue with the greatest possible vigor those illegal drug sales.

pages tightly bound

Mr. WEISS. Dr. Beaulieu states: "Manufacturers that have spe millions of dollars to support the approval of drugs" are "unde standably vexed when violations go unregulated." So his concern that FDA is not evenhandedly pursuing the illegal distribution an sale of veterinary drugs.

[A document containing this statement that Dr. Beaulieu pr pared for a January 24, 1984, briefing with FDA's Acting Commi sioner follows:]

HE COMPLIANCE STATUS OF THE ANIMAL DRUG INDUSTRY IS CURRENTLY NSATISFACTORY. ~~AND IS DETERIORATING.~~ I'VE ALREADY MENTIONED THAT 80-90% OF NIMAL DRUGS CURRENTLY MARKETED ARE IN VIOLATION OF THE ACT. THIS ONDITION PERMEATES THE INDUSTRY AND HAS A SIGNIFICANT IMPACT ON THE DEGREE F COMPLIANCE WITH OTHER PORTIONS OF THE ACT. THERE IS A GENERAL MPRESSION AMONG BVM COMPLIANCE PERSONNEL, BASED ON LONG EXPERIENCE AND OMPARISON OF GMP INSPECTIONS BETWEEN FIRMS THAT MANUFACTURE BOTH HUMAN AND ETERINARY DRUGS IN THE SAME FACILITY AND THOSE THAT MANUFACTURE ONLY ETERINARY DRUGS, THAT THE INDUSTRY HOLDS ITSELF TO A LOWER STANDARD OF ANUFACTURING PRACTICES FOR ANIMAL DRUGS THAN HUMAN DRUGS. HOWEVER, THE CT, THE REGULATIONS AND BVM RECOGNIZE NO LOWER STANDARD FOR ANIMAL DRUG ANUFACTURE. THE GMP STATUS OF THE ANIMAL DRUG INDUSTRY IS NOW, AND HAS RADITIONALLY BEEN, LOWER THAN THAT OF THE HUMAN DRUG INDUSTRY.

ECISIONS REGARDING THE MANUFACTURE AND DISTRIBUTION OF ANIMAL DRUGS APPEAR O BE PRINCIPALLY ECONOMIC IN NATURE, NOT PRINCIPALLY ANIMAL AND PUBLIC EALTH-RELATED. WHEN ECONOMIC PRESSURES INCREASE, SIGNIFICANT EFFORT MAY E DIRECTED TOWARD MAINTAINING OR IMPROVING PROFIT MARGINS BY CUTTING RODUCTION COSTS OR OTHER OVERHEAD COSTS. ADDITIONALLY, PRODUCTS MAY BE ADE TO APPEAR SUPERIOR TO COMPETITIVE PRODUCTS THROUGH FALSE, MISLEADING R OTHERWISE EXAGGERATED PROMOTION. ALL OF THESE EFFECTS ARE CURRENTLY EING OBSERVED IN THE ANIMAL DRUG INDUSTRY. FURTHERMORE, THE EXTENT TO HICH SUCH TECHNIQUES ARE EMPLOYED IS DIRECTLY RELATED TO THE INDUSTRY'S ERCEPTION OF THE AGENCY'S ABILITY TO REGULATE SUCH ACTIVITIES. FAILURE TO E REGULATED ONCE A FIRM RESORTS TO ONE OF THE ACTIONS NOTED ABOVE, REINFORCES THE ACTION AND THE PERCEPTION OF THE AGENCY'S INABILITY TO REGULATE. THE KNOWLEDGE THAT COMPETITORS ARE VIOLATING THE LAW LEADS TO EITHER SIMILAR VIOLATIVE ACTION ON THE PART OF THE MORE REPUTABLE, COMPETITIVELY DISADVANTAGED FIRMS OR TO ~~COMPLAINTS TO THE AGENCY~~ TO DO SOMETHING. SUCH INDUSTRY COMPLAINTS ARE NOW OCCURRING WITH UNPRECEDENTED FREQUENCY. IF THE BUREAU LACKS THE RESOURCES TO RESPOND TO SUCH DIRECT COMPLAINTS, THE RESULTS CAN BE VERY SERIOUS INDEED. (A NUMBER OF THE COMPLAINTS ACTUALLY BEAR AN IMPLIED THREAT TO RESORT TO SIMILAR ACTIVITIES, IF NO ACTION IS TAKEN).

BECAUSE OF THE HIGHLY COMPETITIVE ECONOMIC NATURE OF THE LIVESTOCK INDUSTRY THE RACE HORSE INDUSTRY (FOR WHICH PRODUCTS ARE DEVELOPED SOLELY TO IMPROVE PERFORMANCE OF THE ANIMALS AND NOT FOR ANY THERAPEUTIC PURPOSE), THE MARKET FOR CHEAP OR ILLEGAL DRUGS IS ENORMOUS AND CONTINUES TO MOTIVATE AN INDUSTRY ASSOCIATED WITH ILLEGAL IMPORTATION OF BULK DRUGS AND FINISHED DOSAGE FORMS, ILLEGAL MARKETING OF DOMESTICALLY PRODUCED BULK NEW ANIMAL DRUG SUBSTANCES OR NEW ANIMAL DRUGS (EITHER UNIQUE CHEMICALS OR PURPORTED GENERIC EQUIVALENTS OF NADA APPROVED PRODUCTS), ILLEGAL DISTRIBUTION OF APPROVED OR UNAPPROVED RX DRUGS, AND WIDESPREAD EXTRA-LABEL USE OF DRUGS BY PRACTITIONERS AND PRODUCERS OF FOOD-PRODUCING ANIMALS.

ALL OF THESE VIOLATIVE PRACTICES ARE INTERRELATED, AND FAILURE TO REGULATE IN ONE AREA STIMULATES NON-COMPLIANCE IN OTHERS.

BVM HAS RECENTLY TAKEN THE INITIATIVE TO CURTAIL EXTRA-LABEL USE AND ILLEGAL DISTRIBUTION OF ANIMAL DRUGS IN THE FORM OF POLICY CHANGES AND THREATENED REGULATORY ACTION. IF REGULATORY ACTION DOES NOT ENSUE, THE REGULATED INDUSTRY WILL NOT PERCEIVE THE AGENCY AS A VIABLE DETERRENT TO SUCH VIOLATIVE ACTIVITY AND THE SITUATION MAY DETERIORATE FURTHER.

WE MENTIONED THE MISBRANDED NUTRIENTS PROBLEM AT AN EARLIER MEETING AND IT WAS GENERALLY CONCEDED (AND I AGREE) THAT THESE ARE OF A LOWER PRIORITY THAN SOME OTHER CURRENTLY EXISTING PROBLEMS. IT SHOULD BE NOTED HOWEVER, THAT SUCH AN EXPANDING VIOLATIVE PRACTICE SERVES AS A GLARING EXAMPLE OF AGENCY INACTIVITY AND STRENGTHENS THE PERCEPTION OF A GENERAL INABILITY TO REGULATE. FURTHERMORE, UNLIKE SUCH PRODUCTS FOR HUMANS, THE VIOLATIVE ANIMAL PRODUCTS ARE IN DIRECT COMPETITION WITH APPROVED PRODUCTS WITH THE SAME CLAIMS. MANUFACTURES THAT HAVE SPENT MILLIONS OF DOLLARS TO SUPPORT THE APPROVAL OF DRUGS TO INCREASE THE PRODUCTIVITY OF FOOD-PRODUCING ANIMALS ARE UNDERSTANDABLY VEXED WHEN FORCED TO COMPETE WITH LARGELY UNREGULATED AND MISBRANDED FOODS. UNDERSTANDABLY, SUCH FIRMS ARE BEGINNING TO QUESTION THE WISDOM OF LARGE EXPENDITURES FOR RESEARCH AND DEVELOPMENT OF NEW PRODUCTS WITHOUT SOME ASSURANCE OF A STABLE REGULATORY CLIMATE FOR THEIR INTRODUCTION, (I.E. WITHOUT ASSURANCE THAT FDA CAN PREVENT UNAPPROVED COMPETITION IN THE FUTURE).

IF THE SITUATION IS PERMITTED TO DETERIORATE FURTHER THE ENTIRE NADA APPROVAL PROCESS MAY COLLAPSE.

THE FIELD RECOGNIZES THE NEED FOR ACTION IN THIS AREA AS DEMONSTRATED BY DIRECT STATEMENTS TO THE EFFECT THAT BVM PROGRAMS ARE UNDER-RESOURCED AS WELL AS CONSISTENT OVERBURN IN BVM PROGRAM AREAS. I DOUBT THAT THERE IS ANY AREA IN FDA WHERE A MODEST INCREASE IN RESOURCES COULD HAVE A MORE BENEFICIAL EFFECT, OR WHERE A FAILURE TO INCREASE RESOURCES COULD BE POTENTIALLY MORE DISASTROUS, THAN IN THE ANIMAL DRUG INDUSTRY.

I BELIEVE THE RECORD DEMONSTRATES THAT BVM IS NOW DOING ALL THAT CAN REASONABLY BE EXPECTED WITH ITS EXISTING RESOURCES. IN FACT, WE MAY HAVE DEPENDED TOO LONG ON THE DEDICATION OF THOSE IN THIS AND OTHER BVM PROGRAMS. PEOPLE CAN BE EXPECTED TO FIGHT A HOLDING ACTION AGAINST OVERWHELMING ODDS FOR A LIMITED TIME ONLY, WITHOUT SOME HOPE OF REINFORCEMENTS.

THE BUREAU WILL COME FORWARD WITH SPECIFIC RECOMMENDATIONS IN THE NEAR FUTURE. I ASK YOU TO GIVE THEM VERY SERIOUS CONSIDERATION.

Dr. **Crawford**. No. I do not agree that that was his assertion. He is like all the rest of us; we look forward to the day and hope for the day when no one violates any of the drug distribution laws. And we all want to be as vigorous as we possibly can.

The difficulty is that by the time we solve one problem, another problem crops up. So we must always remain vigilant. And I believe the thrust of his statements were consistent with that.

Mr. **Weiss**. Is it not true that legitimate manufacturers have been reporting the marketing of unapproved veterinary drugs to FDA at an unprecedented rate?

Dr. **Crawford**. I would not say it is unprecedented; no. They have been reporting it and we have been following it up.

Mr. **Weiss**. Again, Dr Beaulieu, who is in charge of surveillance at CVM, has observed that the industry is "eliminating [the] excuse" that FDA has been unable to detect the marketing of unapproved veterinary drugs by reporting such violations to FDA for correction with "unprecedented frequency."

[These statements appear in a memorandum prepared for a July 12, 1984, CVM management meeting, as well as a document prepared for a January 24, 1984, briefing with FDA's Acting Commissioner, both of which are in the record.]

Mr. **Weiss**. In other words, legitimate manufacturers are reporting to you in unprecedented numbers, instances of illegal sale of new animal drugs.

Dr. **Crawford**. What is the date of the Beaulieu memorandum?

Mr. **Weiss**. It is within the last 2 years. It is not, however, specifically dated.

Dr. **Crawford**. But what is the actual date? Because we initiated a program that I believe was in response to that memorandum, which I would like to explain to you. I am not familiar with the memorandum right off the top of my head. So if I could know the date, I could perhaps answer the question better.

Mr. **Weiss**. Well, tell me what, in fact, you have done in response to those complaints you have received.

Dr. **Crawford**. In 1982, we conducted a survey, along with USDA, of some of the specific complaints we were receiving. When we got the results of that survey in, under our field forces of FDA and also from the U.S. Department of Agriculture's Residue Avoidance Program, we initiated a program called the Extra Label Use Program. What that did was instruct veterinarians and other users of animal drugs that because of some problems, including what we believed to be an outbreak of illegal veterinary drug use, we would change the rules accordingly. And we gave them specific instructions that prescription drugs, which are those we have most concern over, could not be sold without a veterinarian/client/patient relationship; and, also, that we did not want drugs being used promiscuously, and we outlined the regulatory steps we would take in that direction.

After that and due to those complaints, we had reason to believe that the drug most often misused was chloramphenicol. In response to chloramphenicol's misuse, we initiated a chloramphenicol enforcement program in concert with field forces and others, and in March 1984, we sent a letter to the Nation's 40,000 veterinarians and also to other selected individuals informing them of the dangers of chloramphenicol and also warning them that it had never been approved for food animal use and that we were going to take extraordinary steps to bring that use under control. And we have and have made the appropriate effort in order to deal with it.

In the wake of that, we have dealt with other illegal drug use. So I believe we have responded to those concerns.

Mr. **Weiss**. What is the PMS Program?

Dr. **Crawford**. Program Management System.

Mr. **Weiss**. As part of the PMS Program, Dr. Beaulieu has written: "Once industry perceives that we have lost the ability to remove unapproved competitive [new animal drugs] from the market, they will either be unwilling to invest the resources to develop or refine their own products or they will simply elect to market the products without approval until we catch them (after which they may perceive we won't do much anyway)."

[This statement appears in a memorandum prepared for a July 12, 1984, CVM management meeting, which is in the record.]

Mr. **Weiss**. Now, is it your testimony that since that and the earlier memorandum were written that your center has gotten the situation well in hand and that there are no longer any problems of widespread distribution of unapproved new animal drugs in the marketplace?

Dr. **Crawford**. They are not completely under control and never have been. We do the best we can to deal with the problem. We have taken extraordinary efforts in order to deal with it and we believe that certain aspects are clearly under control and that other aspects still need more work.

When we initiated that program in 1983, we estimated that it would take several years to bring about the level of compliance that we wanted to achieve. We believe we have made steady progress. We have certainly made steady efforts. And circumstances such as the use of chloramphenicol are improved. There are other problems that we believe are also improving.

Mr. **Weiss**. Dr. Beaulieu has also written: "We're burning our good people and we're only scratching the surface of an industry that has been and remains largely unregulated * * * [I]ndustry's perception of the situation has caused violations to increase in both number and severity * * * Industry is testing us and anyone who thinks that the industry won't sink to the lowest level of compliance they can get away with doesn't appreciate the competitive pressures in the marketplace * * * We *must* improve our regulatory credibility or the whole system will break down."

[This statement appears in a memorandum prepared for a July 12, 1984, CVM management meeting, which is in the record.]

Mr. **Weiss**. Are we on the verge of a system breakdown? Or were we when he wrote that within the last 2 years?

Dr. **Crawford**. It was his statement that we needed to do something and do it fast, and we have responded to that. He, as you know, is essentially in charge of that area. And so, because of his commitment, they are working harder. We also have received permission to acquire 10 additional field personnel to deal with the problem more effectively. And we are working harder in headquarters, also.

Mr. WEISS. Materials prepared for a January 24, 1984, briefing with FDA's Acting Commissioner included the following statement: "A more difficult problem to address is that the industry is not particularly responsive to [CVM] . . . [T]he responses we hear most frequently to requests for correction of violative practices are variations on 'Stick-it-in-your-ear.' "

[The materials referred to follow:]

Goals represent two major functions of PMS-65

1. Regulation of marketed unapproved products
2. Regulation of marketed approved products
3. An obvious means of improving the efficiency of our processing data to take advantage of state of the art technology for doing so.

First goal looks like a typical motherhood and apple pie statement except for that term "substantial." This to some extent depends on the ~~age~~ eye of the beholder. Personally, I am unsatisfied with the current compliance status of the animal drug industry and I believe ~~a great deal of work remains to~~ be accomplished under this PMS.

Compliance Programs:

In my opinion, up until 5 or 6 years ago, BVM didn't pay sufficient attention to its compliance programs. Even though significant advances have been made in CP development, monitoring and evaluation, we're still paying a price for that period of relative inattention. Despite support of PMS 65 programs in principle by the BVM Field Committee and the field in general, in practice, certain Districts are not taking our programs as seriously as we'd like. I believe this is in the process of correction and we intend to have further discussion on this issue (and I believe we'll make further progress) at the BVM/Field Committee meeting on 1-27-84. The need for activity under PMS 65 CPs and the generally supportive attitude of the field is represented by the greater than 50% overburn which has occurred in PMS 65 programs for the past several years.

A more difficult problem to address is that the industry is not particularly responsive to BVM. This may be a general sign of the times, but the responses we hear most frequently to requests for correction of violative practices are variations on "Stick it in your ear." Since we are loath to follow that advice without a fight, we must exercise a good deal of regulatory discretion and choose our fights carefully. One thing that would be of immense value in this regard is better objective information on the compliance status of the industry. We know, for example, that there are approximately 550 veterinary pharm. mfrs. subject to regulation under PMS 65 but it took a surprising amount of effort to arrive at that figure and current systems make it difficult to maintain an accurate inventory.

We believe, based partly on AHI estimates and extrapolations of partial drug listing data, that there are on the order of 20-30,000 vet. pharm. currently on the market. 2-3000 of these are provided for by the 11-1200 currently approved NADA's. Given the nature of vet. pharm and the lack of published literature supporting them, virtually all are NAD's, which means that 80-90% of all vet. drugs currently marketed are in violation of the Act.

When faced with 20,000 potential regulatory actions, it is obvious that we must prioritize our activities and direct our resources to the most significant violations first. In general, our priorities place human safety first (eg. residues from food animal products), animal safety second and ineffectiveness/fraud last, but those need to be further refined. To do so we must get a better idea of the kinds of products and the numbers of products of various kinds currently being marketed. Once we accomplish this, we can more definitively prioritize our workload and direct our field resources to specific products or classes of products produced by specific firms. In addition to being a more effective use of resources, such a regulatory process would be more equitable ~~for the industry. Such data~~ would also provide a basis for proceeding with class action/ FR publications, a process advocated by OGC at various times but which is sufficiently resource intensive that the Bureau needs a solid basis for selecting the most serious problems first.

To address this issue we revised our VDPQ program in FY 83 to direct inspectors to collect for BVM review all product labeling during routine biennial inspections. It will take longer than we'd like (more like 3 years than two) to accomplish this but we will eventually have a reasonably accurate listing of all vet drugs currently marketed to serve as a basis for directing future compliance activities to areas of the greatest concern.

In the meantime, we continue to evaluate those violative situations of which we become aware and to initiate action in those cases which appear to warrant it. We have identified and taken significant steps to curtail a major problem associated with the illegal distribution and extralabel use of products in food-producing animals. Such activity is consistent with our current priorities in that the public health is a major concern. The revision of policy and subsequent publicity has convinced the AVMA to admit that a problem exists and stimulated that organization to establish guidelines for veterinarians which control all but the most prudent extra-label use of drug in food animals. This effort will, we believe, have a positive effect on the vast majority of practicing veterinarians but we recognize that a few will continue to flaunt the canons of ethical practice and the FD&C Act and we are prepared to take regulatory action against these individuals.

Label/Promotional Material Review

In addition to those reg. actions which are recommended by the field based on their assessment of the compliance status of individual firms or products (or arising secondarily from BVM review of specific labels submitted by the field which result in a conclusion that action is warranted), the general label review process will result in directives to the field to pursue action on those products considered significantly violative. A significant number of these label reviews will be quite complex. It is often difficult (and time consuming) just to determine whether a product should be regulated as a food, a device or a drug and whether it might also be considered a biologic or a pesticide and, if so, which agency should regulate the product. If it is subject to FDA jurisdiction is it violative? (The answer to this question is most often, yes). If so, does it warrant the expenditure of limited resources to effect correction? (Much more frequently than we'd like, the answer to this question is, no).

Regulatory Actions

About 75% of BVM's regulatory actions fall under this PMS. In FY 83 these ranged from prosecutions for illegal distribution of DES for veal calves; to injunctions and contempt of injunctions for GMP, NAD and illegal distribution violations; to multi-$100,000 seizures for NAD violations; to numerous regulatory letters on CMP, NAD and illegal distribution charges. I think there is a point worth making here regarding the number of regulatory actions recommended by the Bureau under this PMS relative to those recommended by other parts of FDA. While the absolute numbers may not be impressive, when those numbers are considered relative to the available resources they qre quite impressive~~. I'm not prepared to draw~~ any specific conclusions from this admittedly rough analysis. I think it is generally indicative of sustained performance and dedication on the part of those working on the PMS, and perhaps, to some extent is also a reflection of the general complinace status of the industry. It would appear that the Agency is receiving a substantial return on its resource investment in this PMS and could expect similar returns if it elected to increase that investment. I think the numbers would be impressive even if this was the only function the 66 persons in this PMS performed but these same people (more particularly the 42 hq personnel) also perform all of the other functions on our list.

HHE's/R~~ECALLS~~ecalls

As noted on the previous slide, BVM processes relatively few recalls. I believe this is again representative of the general attitude of the animal drug industry. The industry very rarely spontaneously recalls a product and generally reacts unfavorably to suggestions to do so. In one case in Florida, the recall (which we prompted) consisted of driving around picking up the violative product and replacing it with an equally violative product. This general attitude leaves us with the option of seizure or other direct regulatory action or being satisfied with termination of the violative act with a promise not to repeat it. (Most often we have to be satisfied with the latter).

Consumer, Mfr., Congressional Inquiries and FOI Requests

About 390 of the former and 430 of the latter were processed by BVM last year under this PMS which accounts for about 80% of all such items processed in BVM. Despite the short time frames imposed on Congressionals and FOI requests, relative to other PMS needs which more directly impact on product safety and effectiveness, these functions cannot be considered high priorities. It is fortunate that BVM receives, and therefore has to process, relatively few such inquiries (only about 1/3 to 1/2 as many as the agency average on the same equivalent resource basis used previously).

Veterinary Drug Regis./Listing

BVM has made significant progress in assuming responsibility for drug listing functions from NCDB. The 2 1/2 year backlog of forms has been processed and new forms are being entered "on line" into NCDB's ADP system. Unfortunately, we have to rely on NCDB to retrieve the data because the program is only operable on their equipment by their personnel at this time. BVM has proposed an ADP program to be operated on its new hardware so that it can be self-sufficient in this area. Best estimates are that the info. currently in the system is only 50% accurate so that the proposed system provides for updating via labels collected under our VDPQ program as discussed earlier. Separation of drug registration functions is difficult because until reently there was no basis for identifying whether a firm was a human pharmaceutical mfr., a vet product mfr. (including medicated feeds) or both. The current registration file contains roughly 13,000 feed mills, 500 vet pharm mfr, and 5000 human pharm. mfrs. Thus about 3/4 of the file is ostensibly BVM's responsibility but all the resources are in NCDB (and apparently wouldn't transfer with the function). We are aware that the agency is exploring ways to maintain these functions by contract or by charging user feeds for the service.

Drug Experience Reports

About 2500/year including about 1200 ADRs were reviewed under the PMS last year. As NADA approvals increase, so do DERs-roughly at the rate of 2 1/2 DERs/year/NADA. The NADA rewrite effort corresponding to the NDA rewrite may further increase this number by shifting some work currently performed by preclearance personnel via NADA supplements to PMS 65 personnel under DERs. About 8% of DER reviews result in action.

Reviews include: New studies, ADRs, mfg info, quant. distr. and promo. material.

There is the general impression that the latter is deteriorating relative to compliance w/published regulations. The Bayvet national TV promotion of the Rx drug Proban is a significant example of a general decline.

I believe BVM has been quite effective in developing methods for collecting and analyzing data on animal adverse drug reactions. For example, the VDERP which is unique in the world in collecting numerator and denominator animal ADR data. 4 major veterinary institutions are currently involved. While resource constraints have prevented its full utilization by BVM, ways to share the system in return for access to information gained through its use are currently under review. BVM also has contracts with independent sources of spontaneously reported ADR info which provide for the info. to be forwarded to BVM.

Also under active study is a telephone survey system to gather ADR info. shortly after NADA approval of significant new products.

Regulatory Supplemental NADA Reviews

A frequent action resulting from DER review is a request for and the ultimate submission of regulatory supplemental NADA's to correct a problem discovered thru DER review. Usually this is via labeling or formulation changes or revised (and more stringent) manufacturing practices. There were 89 such supplements reviewed in FY 83. Such reviews can be quite resource intensive. Current examples include: Compudose-an OTC estradiol implant w/mfg problems resulting in increased sexual activity and implant loss (The former would probably be more serious if it weren't for the latter). Topagen-an Rx-OTC steroid antibiotic combination containing a surfactant irritating to the ear canal. ~~Mitaban (amitraz) an Rx~~ topical treatment for demodectic mange w/ stability problems and sufficient unexpected adverse reactis to necessitate additional precautionary info. Eqvalan (ivermectin) an Rx injectable broad spectrum equine anthelmintic with significant serious ADRs caused mainly by injection site Clostridial infections. May ultimately result in NADA withdrawal.

Causal Reviews

This system supports the supplemental NADA approval policy which permits deferral of review of underlying safety and effectiveness data for most NADA supplements pending subsequent review of such data on a problem-oriented basis. Such reviews are, however, extremely resource intensive. (The review on Oxytetracycline injections involved 14 NADAs containing about 150 volumes). Also recently completed or currently under review are: AS-700 (ctc/sulfa combo.), Sulfadimethoxine oral products, several eye powder NADAs, and (via a review by a rehired annuitant) CAP oral solutions. The latter review resulted in a recommendation to withdraw 6 NADAs providing for millions of dollars of chloramphenicol which is labeled for use in dogs but is being diverted to food-producing animals.

NADA withdrawals

Most of the 25 or so/yr. are voluntary based on lack of marketing but some like CAP oral solutions are involuntary and almost invariably result in a request for a hearing which, if granted, (or ordered over our Summary Judgement) consume considerable rsources to carry to completion.

Program-oriented Research

A relatively minor aspect of this PMS due to its nature. Problems are either so acute that they preclude research project development and/or they are product specific and therefore, more appropriately performed by the manufacturer and not at public expense. But some epidemiological research (using VDERP) and some generic tox. studies and literature review on older products such as piperazine are currently ongoing.

Current Resources

Review slide.

Mr. WEISS. Dr. Crawford, is nonenforcement of the law making it more difficult to regulate new animal drug sponsors?

Dr. CRAWFORD. Well, I have never heard of this statement, "stick it in your ear," Mr. Chairman, although there are those elements of any industry that essentially defy enforcement unless presented with a strong regulatory position.

We believe that our voluntary compliance efforts probably reaches the great majority of persons and industries that we regulate, but there are those that need to be taken to court and prosecuted. There always have been and, regrettably, I'm afraid, there always will be.

Mr. WEISS. I assume that you are not questioning that the statement appears in that memorandum.

Dr. CRAWFORD. We have always tried to be open about these kinds of problems, and in presentations for those sorts of conferences, we want everyone to understand that we are in this thing together. We tried to bring together State regulatory enforcement officials, regional officials in other agencies of the Government, USDA, EPA, and also the trade industry associations and professions that we regulate. We have tried to get them all together on this problem.

We had a meeting in Chicago in September 1983, when the first of these memos, I believe, were current. And we got 27 different organizations together, consumers and others, in order to expose the problem as openly and responsibly as we could.

Mr. WEISS. But as of April 1984, Dr. Beaulieu states that the response received from people being asked to correct violations is a variation of "Stick it in your ear." Dr. Beaulieu has written: "In general, the *industry* has become more *contentious* as they have perceived either our will or our ability to regulate to decrease."

[See the memorandum prepared for a July 12, 1984, CVM management meeting, which is in the record.]

Dr. CRAWFORD. Let me say it this way. I think the minority of those persons that need the strong regulatory stand and also the industries do get more contentious as you crack down on them, and we have seen that. We started this program in 1983, as I said, with great visibility, and by early 1984, persons in charge of the program were getting frustrated because they did not see the immediate compliance that they had hoped for. And those sorts of comments and memos reflect that.

I think the strong thing is that—I think the positive thing is that we are and were concerned and that we continue to be with this particular problem.

Mr. WEISS. You earlier testified that staffing levels have remained largely static, with perhaps only a slight increase in resources. Dr. Beaulieu has written, again within the last 2 years; "Obviously, recent resource restrictions have made a bad situation worse * * * We need urgently a 50-percent increase in field and headquarters resources relative to [the] objective" of protecting the public from unapproved new animal drugs.

[See the memorandum prepared for a July 12, 1984, CVM management meeting, which is in the record.]

Mr. WEISS. What was he referring to in that instance?

Dr. CRAWFORD. He was referring to the development of a budg
presentation within FDA in which we were required to develo
three different budgetary positions, depending upon what was a
thorized. One was, what would you do if you got a decrease in pe
sonnel? What would you do if you remained static? And, thir
what would you do if you got an increase?

All the operating units and, also, the PMS system managers,
which is he one, were asked for that kind of information. Many
them, I suspect most of them, indicated that they wanted mor
than 10 percent and that they may need as many as 50 percen
This is a recurring theme. Almost everyone thinks they need mor
personnel. There is just so many personnel that we have and w
have to allocate them.

We have appealed for an increase in field forces and we hav
been awarded increases in field forces just recently; not the 50 pe
cent level, though.

Mr. WEISS. But you do not disagree with Dr. Beaulieu's estimat
that a 50 percent increase is necessary for you to carry out you
field work, do you?

Dr. CRAWFORD. As a manager, I might disagree with it. The ult
mate decision is mine, and I do not believe that we need a 50 pe
cent increase in personnel.

Mr. WEISS. What percentage increase would you think you'
need?

Dr. CRAWFORD. We have been on record as requesting a 5 perce
increase in personnel in fiscal year 1982 for the field, and then 1
percent more recently than that. And the agency is trying ver
hard to accommodate that 19 percent increase. We do not have i
yet, but we have great hopes for it in the next fiscal year. And w
have made that request, Mr. Chairman.

Mr. WEISS. How much of your request has been granted?

Dr. CRAWFORD. We got 10 extra field positions, which is about a
increase of about 5 percent.

Mr. WEISS. My understanding is that the Drug Listing Act
1972 requires FDA to assemble and maintain a current inventor
of all animal drug manufacturers and marketed animal drugs t
ensure, among other things, full and fair enforcement of the ne
animal drug approval requirements of the law. How much progre
have you made in meeting the requirements of the Drug Listin
Act of 1972?

Dr. CRAWFORD. Following the 1972 Act, the agency during tho
years—now, let me hasten to point out that I was not involved i
that, but I think it was the correct thing. They decided that sinc
the listing applied to both veterinary and human drugs, they woul
consolidate those activities within one of those bureaus, either th
Bureau of Drugs or the Bureau of Veterinary Medicine. They de
cided, because it was larger, to consolidate it into the Bureau
Drugs. Then a couple of years ago, the Bureau of Drugs decide
that they could no longer continue the efforts in that regard, an
they returned the responsibility, with the Commissioner's permi
sion, back to CVM. In other words, they subdivided the responsibi
ity. They took human drugs and we were to pick up veterinar
drugs.

We have not gotten very far along with that particular assignment because in the area where it is to be done this is the same area that has to police illegal drug use. And they wanted resources to develop this drug list. I wanted a compendium of drugs, not just for the United States but for the whole world, so that we could know what drug was used where, when, and in all circumstances.

The cost of that, Mr. Chairman, was estimated to be so great, in terms of personnel and resources, that the only way we could deal with it would be to contract it out. We just—you know, placing it in its proper priority, we did not get around to it. We are beginning to make those efforts now. We have recently awarded a contract for an America's drug listing, which will include a domestic drug listing in the amount of about $400,000. So we are finally getting around to it, but we have been very slow. And it is because of prioritization.

Mr. **Weiss**. Tell me when that contract was signed.

Dr. **Crawford**. It was issued—may I ask my colleague?

Mr. **Weiss**. Please.

Dr. **Crawford**. It is in its second year now.

Mr. **Weiss**. And of the estimated 20,000 new animal drugs on the market in the United States, how many have been entered into the FDA's computerized drug listing system? Dr. Guest, would you know that?

Dr. **Guest**. I don't know. My impression is that we are probably 50 percent into the job. I have been able in recent months to receive a fairly accurate list of various classes of drugs, and my impression is that the progress is good, but that we have a ways to go.

Mr. **Weiss**. On July 9 of this year, Dr. Beaulieu informed our staff investigators that approximately 2,500, or 12 percent, of the estimated total of 20,000 new animal drugs have been entered into the agency's computer system. Would that square with your understanding?

Dr. **Guest**. I think, again, Mr. Chairman, it is a question of the 20,000 figure. I think the 20,000 figure is an estimate and an outside estimate on what is in the marketplace. I think we don't have a—I don't think we have an accurate enough number to say that we are 25 percent of the way. My perception is, just looking at pure volume of what sits on the shelf yet to be done, I would have estimated that we are some 50 percent of the way. I am not familiar with Dr. Beaulieu's latest memorandum on that, however.

Mr. **Weiss**. Tell me how this outside contracting situation works. Are these people doing this work away from the agency? Are they doing it at the agency? When do you project that they will complete the job? What are they telling you?

Dr. **Crawford**. The contract is with the College of Veterinary Medicine at Virginia Tech. And they are working—they regularly come to the Center for consultation, but they are accumulating the list, using their resources and facilities and, also, more importantly, their computer facilities.

Mr. **Weiss**. And what are they telling you concerning their projected date for completing the job?

Dr. **Crawford**. It is a 3-year contract. So it is in the second year and we expect results next year.

Mr. **Weiss**. I should say, Dr. Guest, as a comment on the agency estimates of the number of unapproved new animal drugs bein marketed, that Dr. Beaulieu estimated there are 20,000 to 30,00 such drugs. So the 20,000 figure that we have been using is at th conservative end of Dr. Beaulieu's estimate.

[See materials prepared for a Jan. 24, 1984, briefing with FDA Acting Commissioner, which are in the record.]

Mr. **Weiss**. In any event, as of this point, you do not know ho many veterinary drugs have actually been entered on the compu er? Do you think the 2,500 figure is accurate?

Dr. **Guest**. Mr. Chairman, I think we had better check that an give you a precise figure. And then we could submit that for th record.

[The information requested follows:]

About 8,600 are currently entered into the system formerly maintained by th Center for Drugs and Biologics. About 2,200 are currently entered in CVM's syste with about 7,000–8,000 firms still awaiting entry.

Mr. **Weiss**. Fine. We would appreciate that.

Is the failure to list a drug with FDA a prosecutable offens under the Food, Drug, and Cosmetic Act?

Dr. **Crawford**. Yes. We have brought action a number of time recently against firms that marketed a drug without approval. I many cases, Mr. Chairman, these have gotten actually into th courts because the drug firms, in some instances, will claim tha their product should not have to be approved.

Mr. **Weiss**. I am not speaking of approval now. Isn't simply th failure to list a drug, whether or not it has been approved, a pro ecutable offense?

Dr. **Crawford**. It is required by the 1972 Act, not to list, yes; th Listing Act which you mentioned earlier.

Mr. **Weiss**. So even if a manufacturer believes that a veterinar drug does not require premarket approval, it is still obligated t list with you any drug it distributes, is it not?

Dr. **Crawford**. Exactly right.

Mr. **Weiss**. Will you supply for the record the percentage of th 20,000 to 30,000 drugs estimated to be on the market that hav been listed with the agency?

Dr. **Crawford**. Yes, Mr. Chairman.

[The information requested follows:]

About 10,000 animal drug products have been listed with the Agency which ma represent approximately 40 to 50 percent of the total inventory.

Mr. **Weiss**. An August 22, 1983, memorandum of need from th Center's Division of Surveillance states: "Without active enforcement of compliance on our part, [the registration and listing fil will always be incomplete."

[The memorandum referred to follows:]

# MEMORANDUM OF NEED
FROM
DIVISION OF SURVEILLANCE
BUREAU OF VETERINARY MEDICINE
FOOD AND DRUG ADMINISTRATION

CONTACT PERSON: THOMAS J. DOLS, HFV-212 (443-3183)
PROJECT ADVISORS: DR. DAVID DUCHARME, HFV-140 (443-2280)
and
DR. ROBERT BENSON, HFV-320 (443-6954)
PMS: 64
PMS PROGRAM : NEW ANIMAL DRUG EVALUATION
REQUEST DATE : 8-22-83
TYPE OF SERVICES: COMPUTER PROGRAMMING EXPERTISE
TITLE : DEVELOPMENT OF AN ADP PROGRAM FOR A REVISED NADA DATA FILE

A. BACKGROUND

This data file is a single module of a proposed integrated data base system for BVM that, we believe, could be most efficiently developed and operated by ADA-BASE data management programming. Attached is an outline of the plan and structure of the overall ADP system.

Pertinent to information about veterinary drug products that are the subject of a NADA, BVM currently maintains four separate files, much of which cover the material without benefit of common data fields.

1. NADIS FILE - a documents file that includes information about NADA drug products. The file is so structured that it serves the least of BVM's defined needs.

2. HISTORICAL (Ms. MOTT's) NADA DATA FILE - a product information file about NADAs. The data that is captured in this file has been shown to be useful to the users in BVM. This file now needs to be revised to serve our currently defined needs.

3. DER PRINTOUT - a product information file that now includes information on distributor supplement labeling that is covered by an approved NADA.

4. DRUG LISTING (VET) FILE - a product information file on approved and non-approved drug products that are in the market place as disclosed to us by drug manufaturers through the drug registration and drug listing requirements of the FD&C Act. Without active enforcement of compliance on our part, this file will always be incomplete.

There are other files that contain information on marketed veterinary drug products that are not the subject of an approved NADA. Because of the importance of the NADA as a document in BVM and the additional scientific studies contained in a NADA in support of the subject drug products, BVM will always need an accurate and usable NADA data file that is separate from the other files. We intend to develop a separate MARKETED DRUG PRODUCT INVENTORY FILE that includes information on approved NADA drug products to serve our broader regulatory needs. Both files are to be developed with common fields between them. Only the NADA file will include additional fields peculiar to the additional scientific studies contained in a NADA document and to the supplemental applications that update an approved NADA. The approach we have taken in designing a new NADA data file that serves our defined needs is an update of the existing historical (Ms. MOTT's) NADA DATA file.

The basic structure of the NADIS system prevented us from modifying it in any manner that would serve BVM's defined needs for the NADA data. We also recognize that the success of a REVISED NADA DATA FILE will depend upon input coding by the technicians and professionals in SE who are most responsible for review of specific information in the NADA document. The current practice of allowing DCU to independently code all of the data for the NADA file cannot be sanctioned if the accuracy of the file is to be maintained. When the REVISED NADA DATA program is completed, a one-time translation of the NADIS file into the new system will update most of the information in the previously reviewed documents. Thus, we will not have to repeat our current experience with an outside contractor for the NADIS file in converting our files again. The missing data elements can easily be coded by current staffs in SE and S&C. If at the same time BVM obtains microfiche equipment as planned, we will no longer need the NADIS system and an outside contractor to microfiche the documents. The microfiche aspects of NADIS can be maintained by DCU.

B. DATA INPUT REQUIREMENTS

The attachments describe the structure and data fields of the REVISED NADA DATA FILE. The RECORD ID is the NADA number which represents a pool of individual drug products covered by the authority of the NADA in question. The file is divided up into two parts:

1. HEADER INFO which is pertinent to the record as a whole.
2. TABLE OF CONTENTS which gives specific information about each submission (ORIG/SUPPL) to the NADA and its review and outcome. It follows the normal document structure of all NADAs.

The data fields in the HEADER INFO are grouped into the following unique areas:

1. RECORD ID
2. PRODUCT DESCRIPTION
3. CHEM/MFG CONTROL INFO
4. MFG SITE INFO
5. PRODUCT ID INFO
6. DL/MKT INFO
7. PHARMACOLOGICAL INFO
8. CLINICAL INFO
9. HUMAN FOOD SAFETY INFO
10. SAFETY STUDIES SUPPORTING THE NADA

In the attachment, those fields marked with (F) are peculiar to this NADA file and not common to the MKT DRUG PRODUCT INVENTORY FILE while the unmarked fields are common to both files.

The TABLE OF CONTENTS part of the RECORD follows the normal document structure of all NADAs. That is, the information is grouped around the ORIGINAL NADA submission and subsequent supplement numbers.

C. DATA OUTPUT REQUIREMENTS

Attached is an example of the routine NADA output format. This output format will satisfy almost all users of the system. Any special output printouts that may be required can be generated by PCC upon request with minimum amount of programming on BVM's part.

D. SPECIAL REQUIREMENTS OF THE SYSTEM

1. The developed program should be considered a single module of a larger integrated data management system for BVM being proposed for future development that will include a ADR Profile data file, Revised NADA data file, Revised Drug Listing data file, Label Index file, Revised DER data file, Drug Firm Inventory data file, and GMP Experience data file. Thus, we would expect that the ADA-BASE DATA MANAGEMENT system available at PCC could be used in development and operation of the proposed ADP data system.

2. The office of Scientific Evaluation will be primarily responsible for updating and maintaining this data file.

3. The system should be developed for on-line retrieval of data utilizing BVM's DEC-VAX equipment.

4. The edit routine should involve the basic parameters and relationships of the data. The edit correction routine should be user friendly and simple to understand and use.

5. The table of definitions should be easy to revise without causing a major revision of the ADP program.

6. The computer program should be easy to modify in the future for new or different data fields.

7. The developed ADP system should be user friendly and easy to use.

E. STATEMENT OF WORK

1. Study the given ADP requirements and needs; and obtain clarification from the BVM contact person where needed.

2. Feedback to the BVM contact person as to your understanding of the ADP requirements on all aspects of the proposed system.

3. Recommend any changes you wish to suggest about the ADP requirements of the proposed system; provide options and recommendations on the procedures and ADP equipment needed to operate the system; and recommend the design and structure of any coding forms that may be needed for those coding input data.

4. Upon concurrence of the BVM contact person, begin development of the ADP system in accordance with the agreed to plan and understandings.

5. Provide monthly progress reports on the program development indicating the programming phases that are completed; phases being worked on; and any problems encountered and when and how they were resolved.

6. Initiate the completed ADP program; and with the aid of BVM test the system with a demonstration data set. Revise the program where needed.

7. Help BVM in any one-time translation of header information from other BVM data files.

8. Deliver documentation of the completed ADP program and system including, among, other things, a user friendly manual for all parts of the system and a listing of the program.

9. Provide hands-on training to pertinent BVM personnel in operation of all parts of the system.

Andrew J. Beaulieu, DVM

Mr. **Weiss**. Is there in place an intensive compliance program to ensure that registered firms list their drugs with the agency?

Dr. **Crawford**. Dr. Guest is going to respond to that, if he may.

Mr. **Weiss**. Fine. Dr. Guest.

Dr. **Guest**. Mr. Chairman, the program with our field forces calls for the field to visit drug manufacturers on a regular basis, at least every 2 years. And at the time they visit those drug manufacturers, whether they be large or small, part of that assignment is to collect all the labeling used by that firm for animal drugs. Those labels, and sometimes there is quite a large amount of them from any given firm, are all sent in to the headquarters, the Division of Surveillance—Dr. Beaulieu's division, incidentally—for listing and for checking on the propriety and the truthfulness of the labeling that has been picked up by the field forces.

Mr. **Weiss**. There is a finite universe of registered firms that manufacture drugs. So you know for the most part what firms manufacture the vast majority of animal drugs. Isn't that correct?

Dr. **Crawford**. Yes; that is correct. The major firms that manufacture most of them, we have regular inspectional contact with. The difficulty we have, Mr. Chairman, are those small firms that may manufacture only one or two drugs and find that it is, frankly, difficult to comply with the testing requirements. Many times, they feel compelled to market without approval. And it is hard to keep up with them because they develop overnight, sometimes, and other times they change their name, move to other States.

Mr. **Weiss**. If you are dealing with firms on a continuing basis, and they know that you are serious about prosecuting them for failing to list their drugs, regardless of any determination that such drugs require pre-market approval, wouldn't you think you would get more compliance from them?

Dr. **Crawford**. Right. I think, again, we would have that two-tiered—we do have the two-tiered situation-contact with and more compliance. And those that manufacture many of these drugs are companies that we never heard of and you never heard of, and we do not get the listing or the contact with them.

Mr. **Weiss**. But if most manufacturing is done by the major firms, it seems to me that these companies rely, to a great extent, on keeping in the good graces of the regulatory agency. It seems to me that you could advise them that the law is what it is, and that if they don't list their drugs, you are willing to prosecute them.

Dr. **Crawford**. I think you're right. In fact, I know you're right. We need to speed that process along and use it for that purpose.

Mr. **Weiss**. The Drug Listing Act, I understand, also requires FDA to keep a current registry of firms manufacturing new animal drugs. What percentage of those companies have registered themselves with FDA, as required by law?

Dr. **Crawford**. We believe that we have a large number.

I would like to ask Mr. Shane, who is from Kansas City, to respond to that from his point of view, and that is, from the field.

Mr. **Weiss**. Mr. Shane.

Mr. **Shane**. As far as I'm concerned, Mr. Chairman, we have almost 100 percent of all the drug firms or drug manufacturers listed. We occasionally get a manufacturer, though, who will go into business and as soon as we catch up with him he goes out of business and reopens somewhere else. So you occasionally will hav a manufacturer who we are not aware of until we run across hi product and then force him to register.

In general, I think the vast majority of firms are registered.

Mr. **Weiss**. If that is so, it seems that followup to ensure compli ance with drug listing requirements would even be easier becau you now know the companies that manufacture veterinary drug

How many person-years does FDA allocate to achieving compli ance with the requirements of the Drug Listing Act?

Dr. **Crawford**. We will have to submit that for the record. As indicated earlier, it has been a priority that has been overshadowe by more direct intervention in the illegal drug problem, and th number will not be very great. But we will provide it directly fo you.

[The information requested follows:]

About ½ person years is currently devoted to drug listing (marketed animal dr inventory) activities.

Mr. **Weiss**. Thank you.

My understanding, incidentally, is that there are as many a 12,500 firms that are registered with you as manufacturers o animal drugs. Does that square with your understanding?

Dr. **Crawford**. If you count feed mills that have to mix anima drugs, I think the number will be about 12,000.

Mr. **Weiss**. Dr. Beaulieu has written within the last 2 years: "I is pathetic that the purportedly greatest animal drug regulator organization in the world doesn't even know what it is responsibl for regulating."

[See the memorandum prepared for a July 12, 1984, CVM man agement meeting, which is in the record.]

Mr. **Weiss**. He is referring, I assume, to the animal drugs bein distributed in the United States. What, specifically, does FDA pla to do to assure the public that FDA is identifying which new anima drugs leaving residues in its food supply have not been approved a safe for their intended use?

Dr. **Crawford**. Well, what we did, as I mentioned earlier, wa crank up this regulatory program in 1983. We have also asked fo and gotten more field resources, and we have made surveillanc and compliance of these kinds of products the highest priority i the Center for Veterinary Medicine.

In 1982, our highest priority was the new animal drug evaluatio process, in which—and in that year we made some measurabl strides in that direction. Since that time, it has clearly been su veillance and compliance. And we are doing—we are trying to d velop innovative, imaginative new programs to use our resources i order to bring these under control. At the same time, we are moni toring the residue violation picture as carefully as we can. And i unusual developments take place that make it look like we are n making the progress that we projected for ourselves, we branch o and start a new program specifically for that.

I mentioned the sulfa drug problem earlier. Last year we foun that all of a sudden the residue violation rate for sulfamethazin increased. So then we stopped, got with USDA and developed a pr gram for trying to curtail that specific problem, which was th largest problem we had at that time. They have now published for comment in the Federal Register—that is, USDA has—a sulfamethazine compliance program that we worked out with them.

So we keep trying toward the progress that I had projected in that food editors' conference speech, and hoping that we will get there in 2 to 5 years. Just about the time we think things are going our way, Mr. Chairman, we do have something happen that is unusual and unexpected, but we try to deal with that directly.

Mr. Weiss. But the problem, as we have established in the questions and your responses, is that if you have thousands of drugs out there that you are not even aware of because the companies do not list them. It is impossible for USDA to do any kind of monitoring at all because USDA doesn't even know what products are in use, never mind what their residues are.

Dr. Crawford. We have to do a better job of getting them listed, and that is for sure, as you correctly point out. Many of those drugs, though, as I mentioned earlier, are very small volume items. But unless we have reviewed them, we do not know what the level of——

Mr. Weiss. Don't know what the consequences are. Isn't that right?

Dr. Crawford. That's right.

Mr. Weiss. Mr. Shane, would you please briefly state your current position and professional responsibilities at FDA?

Mr. Shane. Yes. I am a regional director of the Food and Drug Administration. I have the responsibility for the enforcement programs in four States, Iowa, Nebraska, Kansas, and Missouri.

Mr. Weiss. And as the director of FDA's Field Committee, you are the field's principal representative on matters dealing with the Center for Veterinary Medicine. Is that correct?

Mr. Shane. That is correct.

Mr. Weiss. Tell us, if you will, what is a prescription legend and when must a veterinary drug carry it.

Mr. Shane. Basically, a prescription legend means that adequate directions cannot be written for that drug. In other words, a lay person could not identify a disease and identify the drug choice for treatment. Therefore, it requires that a veterinarian dispense that drug. He needs to make a diagnosis and dispense the drug.

Mr. Weiss. So that a prescription drug cannot be used because of its toxicity or other potentiality for harmful effect, except under the supervision of a licensed veterinarian. Is that correct?

Mr. Shane. That is correct, sir.

Mr. Weiss. And veterinarians are expected to determine the need for such drugs and to ensure proper administration and monitoring of their use. Is that correct?

Mr. Shane. That is correct.

Mr. Weiss. Is it your sense that veterinary prescription drugs are generally being distributed in accordance with the conditions imposed by their prescription legend?

Mr. Shane. No.

Mr. Weiss. Are you finding that prescription veterinary drugs are being sold illegally?

Mr. Shane. Yes. We have a number of examples of that, sir.

Mr. WEISS. Are veterinarians consistently requiring a prescri tion or an order from a licensed veterinarian before selling pr scription veterinary drugs?

Mr. SHANE. No. They are not.

Mr. WEISS. And why do you think that is?

Mr. SHANE. I think right now it is probably more of a matter economics. We have a situation where we have found that number of veterinarians have opened retail drug distributing pra tices in conjunction with their clinics. They are really in the reta drug business as well as being a veterinarian. Their practices hav been very lax in selling those drugs. Our people have been able go into those retail stores and buy prescription legend drugs fro employees or from the veterinarians themselves, based upon statement that "we needed them to treat an animal."

Mr. WEISS. So, what is happening—if I can just underscore wh you are saying—is that without the legally required order or pr scription from a veterinarian, lay people are walking into veter narian establishments and are receiving prescription animal dru upon request. Is that right?

Mr. SHANE. In a number of places, yes, sir.

I did not want to infer that every veterinarian is doing that ty of practice.

Mr. WEISS. But it is happening on a large scale. Is that correc

Mr. SHANE. It is happening on a large scale; yes, sir.

Mr. WEISS. Do you believe that veterinarians are consistently d termining the need for and supervising the use of these drugs?

Mr. SHANE. I'm sorry; I did not understand your question, sir.

Mr. WEISS. Is it your understanding that veterinarians are co sistently determining the need for and supervising the use of tho drugs?

Mr. SHANE. No. On our basis of our being able to walk in a freely buy those drugs, the veterinarian would not supervise the use. There is no patient relationship, if we did have animals.

Mr. WEISS. Are illegally sold veterinary prescription drugs com monly administered to animals raised for human consumption?

Mr. SHANE. I would say that, yes, they are.

Mr. WEISS. And have you been finding that such drugs are fr quently being used in food-producing animals for unapproved pu poses?

Mr. SHANE. We have instances, yes, where they are being us for unapproved purposes for which they were not registered. W found chloramphenicol being misused, and that drug was only a proved for use in dogs, but it was being used in beef.

Mr. WEISS. And that is a violation of the law, is it not?

Mr. SHANE. That is correct.

Mr. WEISS. In October of last year, FDA added to its Complian Program Guidance Manual a section on the illegal sales proble which states:

> Serious consequences to the public health and to animal health may result fr illegal sales of veterinary Rx drugs. Misuse of drugs in food-producing animals m produce unsafe residues in edible tissue.

[An excerpt from this section follows:]

FOOD AND DRUG ADMINISTRATION
COMPLIANCE PROGRAM GUIDANCE MANUAL

PROGRAM 7365.002

SUBJECT:	**IMPLEMENTATION DATE**
Illegal Distribution of Veterinary Prescription Drugs (FY 85/86/87/88/89)	October 1, 1984
	COMPLETION DATE
	September 30, 1989

DATA REPORTING

PRODUCT CODES	**PROGRAM/ASSIGNMENT CODES**
54, 56, 67, 68, 69	65002

FIELD REPORTING REQUIREMENTS

Where legal action is proposed send required documents to Case Guidance Branch, HFV-236, as directed by the RPM 1-02-13.

PART I - BACKGROUND

The veterinary prescription drug legend "Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian" was established by regulation (21 CFR 201.105), since adequate directions for lay use cannot be written for certain animal drugs which are toxic or have other potential for harm, or which, because of the method of use, are not safe for use except under the supervision of a licensed veterinarian. Accordingly, veterinary prescription (Rx) drugs may be used, prescribed or sold only when a veterinarian has first diagnosed the disease conditions for which the drugs are to be used.

Serious consequences to the public health and to animal health may result from illegal sales of veterinary Rx drugs. Misuse of drugs in food-producing animals may produce unsafe residues in edible tissue. A potentially serious health hazard exists when such drugs are diverted for human use. Treated animals may suffer adverse reactions and side effects when drugs are administered indiscriminately.

Mr. **Weiss**. Mr. Shane, how long have illegal prescription sales been a potentially major regulatory and public health problem?

Mr. **Shane**. That would be a difficult question to answer, Mr. Chairman. Maybe I can put it in some perspective. We have been aware that in the 1950's veterinary drugs were being sold without prescription. However, we also had a major problem in the agency to deal with illegal sale of human prescription drugs, and our forces were dedicated to deal with that problem and not the veterinary problem.

Over the years, it was mainly confined to drugstores and that was the source of veterinary drugs. It came out of the drugstores and started going into peddlers, with their carts. They would buy a van, load it up with drugs, and make the farm-run. We found that becoming more and more of a problem and, recently there is the problem with the veterinary clinics selling drugs. This is, I think, a relatively new issue which has compounded the problem that much more.

Mr. **Weiss**. And, again, if I understand your and Dr. Crawford's testimony, since animal drugs may enter the food chain, they can be as hazardous to our health as human drugs that are misused. Is that correct?

Mr. **Shane**. Yes.

Mr. **Weiss**. Mr. Shane, I understand that approximately 2 years ago you began suggesting that CVM undertake an initiative in this area to learn the scope of the problem. Is that correct?

Mr. **Shane**. That is correct, sir.

Mr. **Weiss**. And when did the first such major initiative take place?

Mr. **Shane**. The first major initiative that took place—if I could refer to my notes?

Mr. **Weiss**. Please.

Mr. **Shane**. Started in fiscal year 1984, which was year before last, 2 years ago.

Mr. **Weiss**. I understand you undertook an undercover operation in the State of Iowa. Is that correct?

Mr. **Shane**. That is correct.

Mr. **Weiss**. Describe that operation for us, if you would.

Mr. **Shane**. The operation involved sending our investigators into veterinary clinics and into dealers or distributors of veterinary drugs. Basically, we had received complaints from the veterinarians that there were illegal sales being made. They mainly complained about the distributors. The distributors complained about the veterinarians.

We visited 37 establishments, which were veterinary clinics, and we were able to make buys at 33 of those establishments, where they sold us prescription drugs without a prescription. Our investigator would simply go in and advise them that we wanted to purchase a drug, a prescription legend drug, one that we would consider a dangerous drug. Basically, they indicated that they did not know us and were a little reluctant to sell. But then they seemed to think that they knew us and went ahead to make the sale.

We also went to 17 dealers, and out of the 17 dealers, 8 of those sold illegally without a prescription.

As a result of that initiative, we worked with the State of Iow This initiative was developed and carried out in coordination wi the Center. We sent regulatory letters to all of those people th were involved in this activity. We worked with the State of Iow the State veterinary associations, and Iowa State University. W held a conference at which Dr. Crawford appeared to lay down th law to these people, telling them that any more illegal sales cou result in prosecution.

We have also recommended prosecution for some of the veter nary clinics because of the type of drugs that we were able to pu chase; and, on that basis, we have recommended prosecution.

Mr. WEISS. And I assume, then, that you would agree with a D cember 12, 1984, CVM memorandum that states th "[I]ndiscriminate sale of prescription veterinary drugs" was "perv sive" throughout eastern Iowa.

[The memorandum referred to follows:]

12/12/84

Illegal Sale of Prescription Veterinary Drugs by Iowa Veterinary Clinics and Drug Distributors

- Strategy -

BACKGROUND

As a result of an indepth investigation by Region VII and St. Louis station in particular, the Agency has documented the indescrimate sale of prescription veterinary drugs by many veterinary clinics and veterinary drug distributors in the eastern part of Iowa covered by St. Louis. The practice is pervasive over this area and in many cases flagrant involving very potent drugs such as chloramphenicol and oxytocin. Statements made during several investigations seem to indicate that this activity is being driven by economics and that it is reasonable to conclude that it may be more widespread than just Iowa.

A meeting was held on November 28, 1984, with the Director, Center for Veterinary Medicine, at which the above facts were presented for discussion. A conclusion was reached that the Agency must take some action to change the behavior of the veterinary community at fault. The credibility of the veterinary drug approval and regulatory process is at stake and the public health implications cannot be ignored. It was decided that a multifaceted program should be developed having the following general elements:

1. Seek out broad based support from Congressional delegations, State agencies, veterinary associations, universities, and the CVM advisory committee.

2. Develop a pilot program for Iowa that will have a regulatory phase and an educational workshop phase.

3. Assure that these activities are well publicized.

4. Check out other areas across the country for similar activity and if necessary use the program in these locations as well depending on its success in Iowa.

STRATEGY PLAN (Pilot Program)

A. St. Louis will review current investigations and identify those flagrant cases involving veterinary clinics, particularly those involving chloramphenicol, which can be immediately recommended for citation. These adequately documented cases will be discussed and will be forwarded to the Center no later than January 15, 1985.

B. Cases involving dealers/distributors will be handled in accordance with current program guidance, but flagrant cases will be identified and submitted as in A above.

C. In addition to the citation recommendations, St. Louis will also prepare regulatory letter recommendations for the remainder of the violators which are adequately documented. Because of the special circumstances involving veterinary clinics the program requirement fo multiple "buys" will be waived. These letters will contain a request to attend a special meeting in Cedar Rapids, Iowa. The precise language will be worked out between the Center and St. Louis. These recommendations should be forwarded to the Center no later than January 15, 1985. The Center will review these recommendations by February 15, 1984.

D. After the above recommendations are forwarded, the Center and the Region will begin preparations for individual meetings with the violators if they choose. The meetings will be held on or about Marc 15, 1985, in Cedar Rapids, Iowa. They will be held by Cliff Shane, Dr. Lester Crawford, and Dr. William Bixler. Hopefully Region VII will gain support from appropriate State agencies/officials, with the State veterinarian hopefully participating in these meetings.

E. The Center and the Region will also begin arrangements for a workshop/open forum for other Iowa State veterinarians which will be held on or about April 1, 1985, in Des Moines, Iowa. The help and cooperation of the Iowa Veterinary Association and State universities and agencies will be sought for holding this meeting which will be open to all. Dr. Crawford and the Center will assist in the contacts with the association and the university.

F. All efforts will be made to have appropriate press coverage of this workshop program nationwide.

IMPLEMENTATION

1. The first step in this strategy is to gain support and head off criticism of this plan.

2. The Center will begin this effort by presenting the problem to its ne advisory committee during the week of December 10, 1985. The presentation will be general and generic in nature so as to not tip the Agency's hand too early. Hopefully, we will get general approval from the committee for action. We can provide the specifics to them later.

3. The next item to be covered is congressional briefings. The Iowa delegation needs to know what the problem is and how the Agency intends to act. In this way, they will be prepared for the expected complaints from constituents.

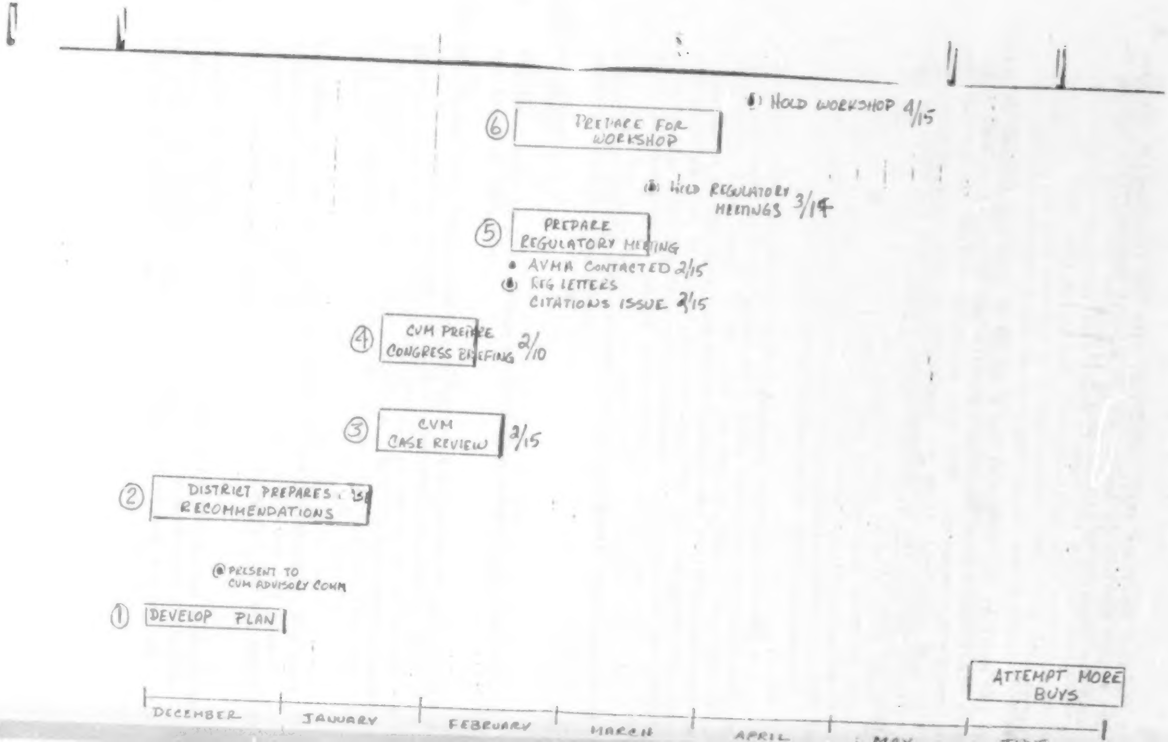
4. Locally the Region can be briefing State authorities and seeking thei support. If all goes well, a good support network will be in place the time the citation/regulatory letters are issued and we can proce with the proposed meetings.

5. It is also important that, concurrent with the veterinarian program, the Agency continue to pursue action against dealers/distributors who also are engaging in illegal sale activity.

EVALUATION

After the meetings are completed and a period of time has elapsed we will need to visit some random veterinary clinics and again try to make some buys (measure-act-measure). This will determine whether our actions had any effect on behavior. If we are successful in this pilot program, then the workshop segment can be converted into a road show and taken to other areas of the country.

(D9/#17)


HOLD WORKSHOP 4/15
⑥ PREPARE FOR WORKSHOP
HOLD REGULATORY MEETINGS 3/14
⑤ PREPARE REGULATORY MEETING
• AVMA CONTACTED 2/15
• REG LETTERS
CITATIONS ISSUE 2/15
④ CVM PREPARE CONGRESS BRIEFING 2/10
③ CVM CASE REVIEW 2/15
② DISTRICT PREPARES RECOMMENDATIONS 15
PRESENT TO CVM ADVISORY COMM
① DEVELOP PLAN
ATTEMPT MORE BUYS
DECEMBER
JANUARY
FEBRUARY
MARCH
APRIL
MAY

Mr. **Shane**. Yes; I would say that's probably a correct statement, sir.

Mr. **Weiss**. And that——

Mr. **Shane**. I would also say that that is probably nationwide in scope.

Mr. **Weiss**. Right. I was going to say that the same December 12 memorandum also states that it is "reasonable to conclude" that these illegal sales "may be more widespread than just Iowa." I assume you agree with that?

Mr. **Shane**. Yes, sir, I do agree with it.

Mr. **Weiss**. Do you have any indications that the problems of Iowa are symptomatic of a national pattern?

Mr. **Shane**. We have some other ongoing investigations right now that I would prefer not to discuss in any detail, Mr. Chairman, because they are ongoing. They seem to confirm our findings in the State of Iowa and in other States.

Mr. **Weiss**. And do you believe that illegal sales by veterinary establishments of powerful prescription drugs have reached epidemic proportions in parts of the country?

Mr. **Shane**. I would say, based upon results of our initial survey in Iowa and our ongoing survey that we have underway, that it would indicate that it is exceedingly high.

Mr. **Weiss**. And the same December 12 memorandum, which reviewed the activities of your region, concluded that these illegal sales threatened "the credibility of the veterinary drug approval and regulatory process" and have "public health implications that cannot be ignored." Do you agree with that assessment?

Mr. **Shane**. Yes. I would agree with that assessment.

Mr. **Weiss**. At this point, we will enter into the record, without objection, some of the reports resulting from FDA's Iowa initiative.

[The reports referred to follow:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date

From Case Guidance Branch, HFV-236
Center for Veterinary Medicine

Subject 85-345-295, Oxytocin Injection
(Regulatory Letter Recommendation dtd 1/9/85)
Iowa Illegal Sale of Vet. Rx Drugs

To

Case Guidance Branch, HFV-236
Homer R. Ransdell, Chief

Brooklyn Veterinary Clinic
Brooklyn, Iowa 52211

REGULATORY LETTER APPROVED

We concur in the issuance of the proposed Regulatory Letter charging 502(f)(1)
for the sale of a veterinary prescription legend drug without a valid
prescription or other order of a licensed veterinarian.

This recommendation is submitted as part of the Iowa Illegal Sale of
Prescription Veterinary Drugs and meets the criteria of that strategy. (It
does not meet the "multiple buy" criteria of CPG 7365.002)

The product involved is Oxytocin Injection. It was purchased on request by
the investigator from a female employee of the firm. She called her "boss"
first because she was not susposed to sell the product to someone she didn't
know. The employee described part of the phone conversation saying the
Federal Drug Agency sometimes sends someone in to buy drugs and this was one
of the drugs they were not susposed to sell, indicating an awareness of the
restriction on sale of this product; and yet, the sale was made with no
additional questions asked. In fact, additional conversation by the employee
after the sale discussed the fact that FDA comes in in all sorts of disguises.

Oxytocin is the subject of 21 CFR 522.1680. The conditions of approval limit
this drug to use by or on the order of a licensed veterinarian. Adequate
directions for lay use cannot be written. It is exempt from this requirement
only when sold on the order of a licensed veterinarian. No such order exists
and no veterinarian/client/patient relationship has been established. The
Regulatory Letter is appropriate.

We agree that the Regulatory Letter should issue to Drs. Hamby and Rickard
only, since Dr. Taylor was only an associate and no longer employed at the
firm by this date.

cc: HFV-200
HFV-230
HFV-236(HR)(RL-5-059)
GJDUNNAVAN:1/29/85:dp:1/30/85draft
GJDUNNAVAN:1/31/85:dp:1/31/85final

Gloria J. Dunnavan
Consumer Safety Officer

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Memorandum

Date

From Case Guidance Branch, HFV-236

Subject 84-495-712, Oxytocin Injection
85-495-719, Estrumate
(Re: St. Louis Station's recommendation of 1/9/85)

To Case Guidance Branch, HFV-236
Homer R. Ransdell, Chief

Mediapolis Veterinary
Clinic P.C.
Mediapolis, Iowa

REGULATORY LETTER APPROVED

84-495-712 documents the sale on July 23, 1984, of one 100 ml bottle of Anpro Pharmaceutical's brand of Oxytocin Injection. Investigator simply requested the product and it was sold to by an unidentified woman with no mention of the necessity for a veterinarian's order.

85-495-719 documents the sale on October 22, 1984, of one 20 ml bottle of Estrumate. Investigator requested Bovilene or Lutalyse. These were not in stock but was told Estrumate is the same thing. There was no mention of the drug's prescription status. The investigator was in disguise at the time of this purchase. Estrumate labeling includes a warning against handling by women of child-bearing age since Estrumate may cause abortion.

On August 24, 1984, Investigator attempted to purchase chloramphenicol and oxytocin at this clinic but was refused.

Anpro's Oxytocin Injection is manufactured by Anthony Products Company under their unapproved NADA 130-136. It is however labeled with the veterinary prescription legend.

Estrumate is the subject of approved NADA 113-645 and 21 CFR 522.460. The veterinary prescription legend, with which the sampled product was labeled, is a condition of approval. This is reflected by the regulation.

The Regulatory Letter should be issued as proposed.

Donny Dean
Consumer Safety Officer

cc: HFV-200
HFV-230
HFV-236(HR/RL 5-073)
DDEAN:2/7/85:dp:2/8/85draft
DDEAN:2/8/85:dp:2/8/85final

READEX
FICHE

CDF

1. FLAG
CP 7365.002 - Do not strip label - Hold without analysis

2. TYPE SAMPLE

3. SAMPLE NUMBER
8 4 -495-712

4. CF NO.

5. JO-TA

6. COUNTY

7. DATE COLL
7/23/84

8. PRODUCT CODE
68SCD20

9. RESP FIRM
D

10. PROGRAM ASSIGN CODE
1. 65002
2.
3.

11. HOURS
1. 1
2.
3.

12. RELATED SPL
None

13. PC
2

14. COLL NO.
203

15. SPLING DIST
STL

16. COLL DIST
STL

17. PRODUCT NAME AND IDENTIFICATION *(Quote pertinent labeling including firm name and address)*
Oxytocin Injection in glass bottle labeled in part:"...100 ml. Sterile XXXXXXX...OXYTOC INJECTION 20 U.S.P. Units per ml...CAUTION: Federal law...Manufactured For Anpro Pharmaceutical Arcadia,CA 91006...DOSAGE...6345 2/86...".

18. REASON FOR COLLECTION *(Indicate analysis needed & document assignment. Include CP No. and/or Assignment No. if applicable.)*
Illegal Distribution of Vet RX Drugs. Do not strip label. Hold without analysis.

19. MFG CODES *(Labels, pkg. shipping containers)*
6345 2/86

20. MANUFACTURER *(Name, address & ZIP)*
unknown

21. SHIPPER *(Name, address & ZIP)*
unknown

22. DEALER *(Name, address, ZIP & telephone)*
Mediapolis Veterinary Clinic P.C.
Hwy 61
Mediapolis, Ia. 52637
319/394-3108

23. SIZE OF LOT FROM WHICH SAMPLED
unknown

24. EST VALUE
unknown

25. RECEIPT ISSUED
FDA472 ☐ FDA484 ☐ NONE XXX

26. DATE SHIPPED & DOC REF
unknown

27. DESCRIPTION OF SAMPLE AND METHOD OF COLLECTION *(Number and size of units, etc.)*
Sample purchased undercover by this investigator as a person off the street. Sample purchased OTC. The sample consisted of 1 bottle of product described in #17 above. See also remarks.

28. HOW PREPARED
Bottle label identified as per #29. Bottle placed into paper bag and sealed 7/23-31/84. On 7/31/84 seal was broken by this investigator and labeling was photocopied and attached to this CR. The bottle was placed into a paper bag and (cont)

29. COLL IDENT ON PKG AND/OR LABEL
"84-495-712 7/23/84 GAL"

30. COLLECTOR'S IDENTIFICATION ON SEAL
"84-495-712 7/31/84

31. SAMPLE DELIVERED TO
US Postal Service
St. Louis, Mo. 63102

32. DATE DELIVERED
8/9/84

33. LAB
KAN

34. LAB W/SPLIT SAMPLE
NA

35. ORIG C/R & RECORDS TO
STL-STA

36. RCDS OBTAINED

a. INVOICE NO. AND DATE
Dealer #None dtd 7-23-84

b. SHIPPING RECORD *(B/L, F/B, Waybill, Affidavit, etc.)* NO. AND DATE
none

c. OTHER DOCUMENTS *(Affidavits from dealers, etc.)* SIGNER'S NAME AND DATE
X Dealer Receipt attached

37. REMARKS *(If additional space is needed, attach Form FD 464a, C/R Continuation Sheet)*
28. officially sealed as per #30 with FD525 attached. Sample placed into box with filler and shipped as per #s 31-33. Seal dtd 7/23-31/84 attached.
23,27 Upon entering this Clinic I was greeted by a woman approx. late 40's, 5'8'', with greying hair, who asked if she could help me. I told her that I needed a small bottle of Oxytocin. She left the front counter area that she had been standing behind and(cont)

38. CONSUMER COMPLAINT NO.
NA

39. AMT. $
7.95
CRED. ☐ CA ☒ V ☐ R ☐

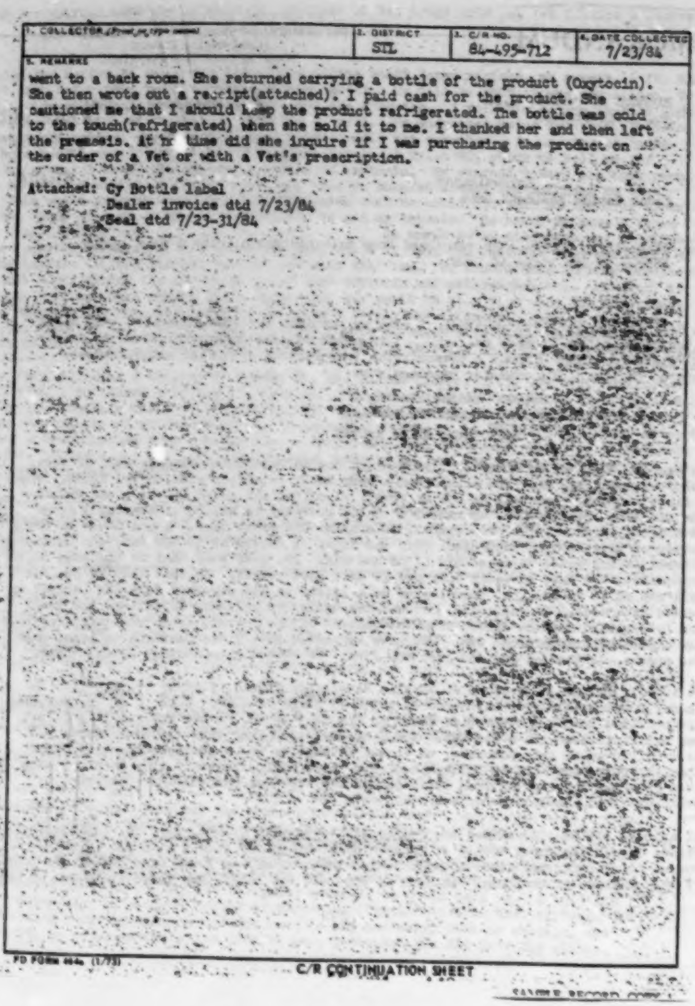
40. 704(a) SPL
YES ☐ NO ☒

41. COLLECTOR *(Typed name and signature)*

FORM FDA 464 (4/82) PREV ED MAY BE USED.

COLLECTION REPORT

SAMPLE RECORD COPY 1



1. COLLECTOR (Print or type name)	2. DISTRICT STL	3. C/R NO. 84-495-712	4. DATE COLLECTED 7/23/84

5. REMARKS

went to a back room. She returned carrying a bottle of the product (Oxytocin). She then wrote out a receipt(attached). I paid cash for the product. She cautioned me that I should keep the product refrigerated. The bottle was cold to the touch(refrigerated) when she sold it to me. I thanked her and then left the premesis. At no time did she inquire if I was purchasing the product on the order of a Vet or with a Vet's prescription.

Attached: Cy Bottle label
Dealer invoice dtd 7/23/84
Seal dtd 7/23-31/84

FD FORM 464a (1/73) C/R CONTINUATION SHEET

SAMPLE RECORD COPY

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Richard D. Turner, S.I.
St. Louis Station

DATE: September 7, 1984

REFER TO:

RECEIVED
SEP 1 2 1984
STLSTA

FROM : Investigator
Cedar Rapids Resident Post

SUBJECT: Attempts to purchase Rx vet drugs from multiple vet clinics & farm supply stores in the state of Iowa.

On 8/24/84, per your instructions, I used my personal car (two-tone blue 1979 Dodge Aspen bearing Iowa license no.) in order to make undercover attempts to buy Rx veterinary drugs without a prescription from various specified establishments located in Iowa. POA odometer readings were:

66,088 ending reading
65,822 beginning reading
: 266 total miles driven

At approx. 10:10am, on 8/24/84, I stopped at Louisa Veterinary Clinic, Hwy. 92 West, Columbus Junction, IA. The clinic had a very small reception area in the front. When I first arrived, there was no one up front. I called and asked if there was anyone there. Soon after, a man, approx. 5'6" tall, probably in his 50's, wearing a green work apron which bore the vet symbol, came up to the front room. I had taken an empty bottle of Viceton chloramphenicol into the firm. I showed it to the man, who introduced himself as Dr. Lowe. I asked him if he had any. Dr. Lowe said that he had some chloramphenicol, but that he would only use it as a last resort. He said that he could not sell any of it to me. Dr. Lowe showed me a letter he had received from BVM (signed by Lester Crawford). He indicated that was the basis for refusing to sell me the drug. Dr. Lowe stated that he agreed with the content of the letter, which basically described how unsafe chloramphenicol was. Dr. Lowe suggested that I use Gentocin to treat hogs for scours. I thanked him and left the firm. We should make another attempt here.

At approx. 10:40am, I stopped at Wapello Veterinary Clinic, Highway 61, Wapello, IA. There, I purchased Oxytocin, Gentocin and 2/15 gauge needles. Details of the purchase are provided in the Continuation Sheet to C/R 84-354-156. I was charged $16.40, but was not furnished with a receipt. The 2 needles are being held at Cedar Rapids R.P. As a follow-up to this purchase, we should attempt to buy a prescription drug other than Oxytocin, Gentocin or Chloramphenicol. Apparently, the only time that Gentocin is a prescription item is when it is prescribed for dogs (according to information available from the Center for Vet Medicine).

At approx. 11:15am, I visited the Mediapolis Veterinary Clinic, Hwy. 61, Mediapolis, IA. There, I took the empty bottle of Viceton chloramphenicol inside with me. I walked in, turned to my left, and asked a woman behind the counter, as I was handing her the bottle, if they had any of the drug. As soon as she read the label, she immediately got up and called the matter to the attention of one of the staff Veterinarians, an approx. 6 ft. man, with dark hair, thin, with somewhat sunken cheeks. He told me that it was now illegal to sell chloramphenicol. He asked what I used the drug for. I told him scours in baby pigs. He asked what kind of scours. I told him E. coli. He suggested using Gentocin, tylosin, & mentioned several other antibiotics which I could not remember. In an attempt to remain inconspicuous, I asked him for a small bottle of Tylan 50, which he sold me for $5.90. Then, I asked the man for a bottle of Oxytocin. He started toward the back room, asking me if I wanted it for my sows, but then he wheeled around and informed me that Oxytocin was a prescription item. He indicated that he could not sell me the drug since he had never seen me or had an opportunity to see my animals. He asked my name & where I was from. I told him . He asked me if Alburnett was in Minnesota (possibly confusing it with Albert Lea, MN.). I told him that the town was north of Cedar Rapids. I then thanked the vet and left the firm. We should make another purchase attempt here, asking for something other than Oxytocin and chloramphenicol. However, it appears that our best chance for a successful buy would be at a time when the Veterinarians were not present, and probably by using a female investigator. Many of the firms I visited appeared to be highly suspicious of a male stranger attempting to purchase a prescription drug. NOTE: The bottle of Tylan 50 is being held under FDA seal at CHRP.

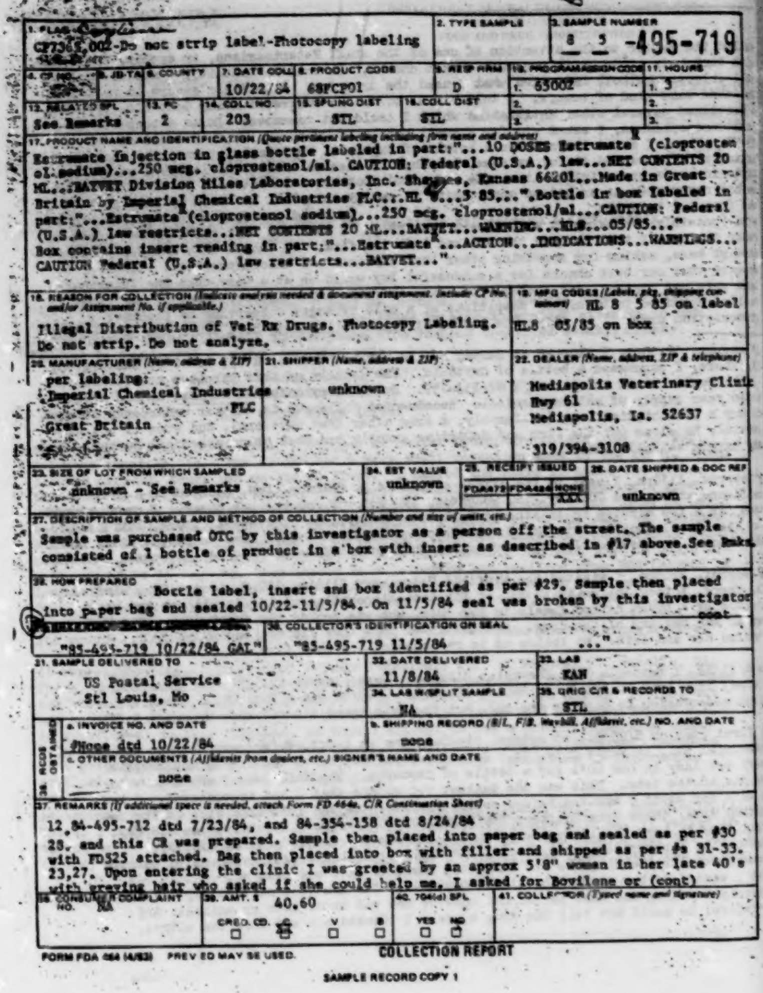
At approx. 12:10pm, I stopped at Summer St. Rd. Animal Clinic, Rt.5, Box 872, Burlington, IA. There, I purchased a bottle of Oxytocin. The details of this purchase are furnished the Continuation Sheet to C/R 84-354-159. Dr. Skelley informed me that he had about a two year supply of chloramphenicol. Recommended follow-up is another undercover attempt to buy a prescription drug (preferably, a drug other than Oxytocin), and even if not successful, to close out the firm and determine exactly how much chloramphenicol he has. He may have a seizable amount.

At approx. 1:10pm, I went to the office of Donald P. Shannon, DVM, located in a private residence at P.O. Box 70, Hwy. 16, Houghton, IA. However, no one was there. I drove around town for a few minutes in an attempt to locate the typical "porta-vet" truck, but I did not see it. I went back to Dr. Shannon's place at about 1:20pm, but there was still no one there. I subsequently returned to Dr. Shannon's office on 8/31/84 (discussed later).

At approx. 2:05pm, I visited the Winfield Veterinary Clinic, 112 S. Locust St., Winfield, IA. There, I took the empty bottle of Viceton chloramphenicol inside with me and was greeted by a brown haired female in her 30's, who was behind the front desk. I asked her if she had any of the drug. She indicated that they did not carry the drug. I thanked her and left. No follow up is recommended for this firm.

On 8/25/84, I rented a 1984 Chevrolet Citation, Iowa license no. XHC-972 (Linn County plates) from Avis at the Cedar Rapids Airport. 8/25/84 was a Saturday. I had a 9 o' clock reservation to pick up the car, but the Avis agent did not show up until 9:57am.

My first stop on 8/25/84, at approx. 11:20am, was at L.P.C. Veterinary Clinic, 105 Commercial St., La Porte City, IA. I went inside, turned to the right, and asked a heavy set lady in her 60's for a bottle of Oxytocin. She said that I would have to see one of the Vets. This was the busiest vet clinic that I had encountered. I had to wait for about 5 minutes before seeing the vet. On the left hand side of the reception area, there were quite a few animal health products on shelves on display. I had time to look the items over, but did not see any Rx products on display. Eventually, a heavy set male, about 5'10" tall, with short light brown hair, wearing green coveralls (bearing the vet insignia) asked if he could help me. I told him that I wanted to buy a small bottle of Oxytocin. The man told me that Oxytocin was a prescription drug and that he did not know me and had never seen my animals, and therefore, he could not sell the drug to me. I thanked him and left the clinic.



1. FLAG Compliance
CP7363.002-Do not strip label-Photocopy labeling

2. TYPE SAMPLE

3. SAMPLE NUMBER 8 5 -495-719

4. CP NO.	5. JD-TA	6. COUNTY	7. DATE COLL	8. PRODUCT CODE	9. RESP FIRM	10. PROGRAM/ASSIGN CODE	11. HOURS
[illegible]			10/22/84	68FCP01	D	1. 63002	1. 3
						2.	2.
						3.	3.

12. RELATED SPL	13. PC	14. COLL NO.	15. SPLING DIST	16. COLL DIST
See Remarks	2	203	- STL	STL

17. PRODUCT NAME AND IDENTIFICATION *(Quote pertinent labeling including firm name and address)*
Estrumate injection in glass bottle labeled in part:"...10 DOSES Estrumate® (cloprostenol sodium)...250 mcg. cloprostenol/ml. CAUTION: Federal (U.S.A.) law...NET CONTENTS 20 ML...BAYVET Division Miles Laboratories, Inc. Shawnee, Kansas 66201...Made in Great Britain by Imperial Chemical Industries PLC...HL 8...5 85...".Bottle in box labeled in part:"...Estrumate®(cloprostenol sodium)...250 mcg. cloprostenol/ml...CAUTION: Federal (U.S.A.) law restricts...NET CONTENTS 20 ML...BAYVET...WARNING...HL8...05/85..." Box contains insert reading in part:"...Estrumate®...ACTION...INDICATIONS...WARNINGS... CAUTION Federal (U.S.A.) law restricts...BAYVET..."

18. REASON FOR COLLECTION *(Indicate analysis needed & document assignment. Include CP No. and/or Assignment No. if applicable.)*
Illegal Distribution of Vet Rx Drugs. Photocopy Labeling. Do not strip. Do not analyze.

19. MFG CODES *(Labels, pkg, shipping containers)* HL 8 5 85 on label
HL8 05/85 on box

20. MANUFACTURER *(Name, address & ZIP)*
per labeling:
Imperial Chemical Industries PLC
Great Britain

21. SHIPPER *(Name, address & ZIP)*
unknown

22. DEALER *(Name, address, ZIP & telephone)*
Mediapolis Veterinary Clinic
Hwy 61
Mediapolis, Ia. 52637
319/394-3108

23. SIZE OF LOT FROM WHICH SAMPLED
unknown - See Remarks

24. EST VALUE
unknown

25. RECEIPT ISSUED

FDA472	FDA484	NONE
		XXX

26. DATE SHIPPED & DOC REF
unknown

27. DESCRIPTION OF SAMPLE AND METHOD OF COLLECTION *(Number and size of units, etc.)*
Sample was purchased OTC by this investigator as a person off the street. The sample consisted of 1 bottle of product in a box with insert as described in #17 above.See Rmks.

28. HOW PREPARED
Bottle label, insert and box identified as per #29. Sample then placed into paper bag and sealed 10/22-11/5/84. On 11/5/84 seal was broken by this investigator cont

29. [illegible]
"85-495-719 10/22/84 GAL"

30. COLLECTOR'S IDENTIFICATION ON SEAL
"85-495-719 11/5/84 ..."

31. SAMPLE DELIVERED TO
US Postal Service
Stl Louis, Mo

32. DATE DELIVERED
11/8/84

33. LAB
KAN

34. LAB W/SPLIT SAMPLE
NA

35. ORIG C/R & RECORDS TO
STL

36. RCDS OBTAINED
a. INVOICE NO. AND DATE
#None dtd 10/22/84

b. SHIPPING RECORD *(B/L, F/B, Waybill, Affidavit, etc.)* NO. AND DATE
none

c. OTHER DOCUMENTS *(Affidavits from dealers, etc.)* SIGNER'S NAME AND DATE
none

37. REMARKS *(If additional space is needed, attach Form FD 464a, C/R Continuation Sheet)*
12, 84-495-712 dtd 7/23/84, and 84-354-158 dtd 8/24/84
28, and this CR was prepared. Sample then placed into paper bag and sealed as per #30 with FD525 attached. Bag then placed into box with filler and shipped as per #s 31-33.
23,27. Upon entering the clinic I was greeted by an approx 5'8" women in her late 40's with greying hair who asked if she could help me. I asked for Bovilene or (cont)

38. CONSUMER COMPLAINT NO. NA

39. AMT. $ 40.60
CRED. CD. ☐ C ☒ V ☐ B ☐

40. 704(a) SPL
YES ☐ NO ☐

41. COLLECTOR *(Typed name and signature)*

FORM FDA 464 (4/83) PREV ED MAY BE USED.

COLLECTION REPORT

SAMPLE RECORD COPY 1

1. COLLECTOR (Print or type name)	2. DISTRICT STL	3. C/R NO. 85-495-719	4. DATE COLLECTED 10/22/84

5. REMARKS

23,27 cont Lutalyse. She said that they didn't stock those but that they had Estrumate which was the same thing. She asked what it was for. I said that I didn't know - he just told me to come in and get some - he has cattle. She then went into a back room and came forward with a man approx 5'6", dark hair, ~~[illegible]~~ 38 yr old. She then asked my name. I told her it was for The man then said that Estrumate was the same as Bovilene. ~~[illegible]~~ I said that I would take it. He said to bring it back if it wasn't what he wanted. He said to ~~[illegible]~~ just follow the insert. The woman then wrote out the invoice. She handed me the box of product with bottle & insert. I paid cash, then left the premises. At no time did either of them question me concerning a vet order or Rx.

Attached: Dealer Invoice(Receipt)# None, dtd 10/22/84
Seal dtd 10/22-11/5/84

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Date

From Case Guidance Branch, HFV-236
Center for Veterinary Medicine

Subject 84-495-711, Oxytocin Aqueous Solution
84-354-159, Oxytocin Injection
85-345-287, Lutalyse Sterile Solution
(Re: St. Louis Station's recommendation of 1/9/85)

To Case Guidance Branch, HFV-236
Homer R. Ransdell, Chief

Summer St. Rd.
Animal Clinic
Burlington, Iowa

REGULATORY LETTER APPROVED

84-495-711 documents the sale on July 23, 1984, of a 100 ml bottle of Tech America's brand of Oxytocin. Investigator simply requested the product and it was sold to with no request for any veterinarian's authorization. The employee of the clinic who made this sale was an unidentified woman.

84-354-159 documents the sale on August 24, 1984, of a 100 ml bottle of Sussex Drug Company's brand of Oxytocin. Investigator requested and was sold this product by an individual who identified himself as Dr. Skelley. Dr. Skelley did ask the investigator why he wanted the drug, but he made no mention of its prescription status, other than identifying it as such on the invoice, and he made no mention of being unable to prescribe the drug without having examined the animals to be treated.

The investigator also requested to purchase chloramphenicol. Dr. Skelley acknowledged that he had about a two year supply, but refused to sell it to the investigator. He stated he would sell it only to people he knew or people who knew how to use the drug, since he would be responsible for any tissue residues. St. Louis Station is still investigating his sale of chloramphenicol.

85-345-287 documents the sale on October 16, 1984, of one 30 ml bottle of Lutalyse. Investigator purchased the drug from two unidentified females, one of whom introduced herself as a veterinarian. Investigator was in disguise at the time this purchase was made. Lutalyse is labeled with a warning against contact by pregnant women. The drug was sold with no mention of the necessity for the prescription or other order of a practicing veterinarian.

Tech America's Oxytocin is the subject of approved NADA 109-305 and 21 CFR 522.1680. Sussex's Oxytocin is the subject of approved NADA 46-822 and 21 CFR 522.1680. Lutalyse is the subject of approved NADA 108-901 and 21 CFR 522.690. The veterinary prescription legend, with which all three products were labeled as sampled, is a condition of approval. This is reflected in the respective regulations.

The Regulatory Letter should be issued as proposed.

Donny Dean
Consumer Safety Officer

cc: HFV-200
HFV-230
HFV-236(HR)(RL5-077)
DDEAN:2/4/85:dp:2/5/85draft
DDEAN:2/5/85:dp:2/5/85final

8-12-84
cab

1. FLAG CP 7365.002 - Do not strip label - Hold Without Analysis				2. TYPE SAMPLE	3. SAMPLE NUMBER 84-495-711	
4. CF NO.	5. JD-TA	6. COUNTY	7. DATE COLL 7/23/84	8. PRODUCT CODE 68FCN20	9. RESP FIRM D	10. PROGRAM ASSIGN CODE 1. 65002 2. 3. / 11. HOURS 1. 3 2. 3.
12. RELATED SPL None	13. PC 2	14. COLL NO. 203	15. SPLING DIST STL	16. COLL DIST STL		

17. PRODUCT NAME AND IDENTIFICATION (Quote pertinent labeling including firm name and address)
Oxytocin Injection in glass bottle labeled in part:"...OXYTOCIN...CAUTION: Federal law ...NET CONTENTS: 100ml...INDICATIONS:...ADMINISTRATION...DOSE...3165B 6-85...EACH ml CONTAINS: Oxytocin (synthetic) 20 USP units...Keep refrigerated: 36-46°F... Manufactured for TechAmerica Group,Inc Elwood,KS 66024...".

18. REASON FOR COLLECTION (Indicate analysis needed & document assignment. Include CP No. and/or Assignment No. if applicable.)
Illegal Distribution of Vet RX Drugs. Do not strip label. Hold without analysis.

19. MFG CODES (Labels, pkg, shipping containers)
3165B 6-85

20. MANUFACTURER (Name, address & ZIP)
unknown

21. SHIPPER (Name, address & ZIP)
unknown

22. DEALER (Name, address, ZIP & telephone)
Summer St. Rd.Animal Clinic
Rt.5 Box 872
Burlington,Ia. 52601
319-752-1566 or 372-2504

23. SIZE OF LOT FROM WHICH SAMPLED
unknown - See Remarks

24. EST VALUE
unknown

25. RECEIPT ISSUED
FDA472	FDA484	NONE
		XXX

26. DATE SHIPPED & DOC REF
unknown

27. DESCRIPTION OF SAMPLE AND METHOD OF COLLECTION (Number and size of units, etc.)
Sample purchased undercover by this investigator, as a person off the street. Sample purchased OTC. The sample consisted of 1 bottle of product described in #17 above. See also remarks.

28. HOW PREPARED
Bottle label identified as per #29. Bottle placed into paper bag and sealed 7/23-31/84. On 7/31/84 seal was broken by this investigator and labeling was photocopied and attached to this CR. The bottle was placed into a paper bag and (cont.)

29. COLL IDENT ON PKG AND/OR LABEL
"84-495-711 7/23/84 GAL"

30. COLLECTOR'S IDENTIFICATION ON SEAL
"84-495-711 7/31/84 ..."

31. SAMPLE DELIVERED TO
US Postal Service
St. Louis, Mo. 63102

32. DATE DELIVERED
8/9/84

33. LAB
KAN

34. LAB W/SPLIT SAMPLE
NA

35. ORIG C/R & RECORDS TO
STL STA

36. RCDS OBTAINED
a. INVOICE NO. AND DATE
Dealer #12246 dtd 7/23/84

b. SHIPPING RECORD (B/L, F/B, Waybill, Affidavit, etc.) NO. AND DATE
none

c. OTHER DOCUMENTS (Affidavits from dealers, etc.) SIGNER'S NAME AND DATE
none

37. REMARKS (If additional space is needed, attach Form FD 464a, C/R Continuation Sheet)
28. officially sealed as per #30 with FD525 attached. Sample placed into box with filler and shipped as per #s 31-33. Seal dtd 7/23-31/84 attached.
23,27 Upon entering this Clinic I was greeted by a woman approx. 25 yr old,5'6'',blond hair,who asked if she could help me. I told her I needed a small bottle of oxytocin. A boy approx 10 yr old who was behind the counter with her at the time left the (cont.)

38. CONSUMER COMPLAINT NO. NA

39. AMT. $ 6.24
CRED. CD. ☐ C ☐ V ☐ S ☐

40. 704(a) SPL
YES ☐ NO ☐

41. COLLECTOR (Typed name and signature)

FORM FDA 464 (4/83) PREV ED MAY BE USED.

COLLECTION REPORT

SAMPLE RECORD COPY 1

1. COLLECTOR (Print or type name)	2. DISTRICT	3. C/R NO.	4. DATE COLLECTED
	STL	84-495-711	7/23/84

5. REMARKS

front office area and went to a back room. He came forward carrying the bottle of sampled product. He had not been told by the woman to get the product. He merely went to get it when I mentioned the product name. The woman then wrote up a receipt (#12246 dtd 7/23/84-attached). I paid cash for the product. I thanked her and then left the premesis. At no time did she ask if I had a Vet prescription or was purchasing the product on the order of a Vet. Also the bottle of product was warm to the tough when it was sold to me(not under refrigeration).

Attached: Cy bottle label
Dealer Receipt(invoice) #12246 dtd 7/23/84
Seal dtd 7/23-31/84.

1. COLLECTOR (Print or type name and Signature)	2. DISTRICT STL-STA	3. C/R NO. 84-954-159	4. DATE COLLECTED 8/24/84

5. REMARKS

Block 27 (Continued):

I entered the dealer firm at approx. 12:10pm on 8/24/84 and was greeted by a gray haired man in his 40's, stockily built, about 5'10" tall. He said that he had not seen me before & introduced himself to me as Dr. Skelley, shaking my hand. I asked Dr. Skelley for a small bottle of Oxytocin. He indicated that he only had the 100 ml. size. I said that was fine. As he started walking toward the back room, he casually asked me what I wanted the drug for. I said for my sows. He said OK and told a small boy to retrieve a bottle of Oxytocin from an unseen location (possibly the basement). When Dr. Skelley gave me the bottle, it appeared to be cool, but definitely not refrigerated. I casually told Dr. Skelley that I had been looking "all over" for some chloramphenicol, and that was why I was so far south of my farm. I gave my address as Alburnett, IA. Dr. Skelley told me that he had about a 2 year supply of chloramphenicol but that he would only sell the drug to people he knew, or to people [redacted] who knew how to use it, since he would be responsible for any residues. Dr. Skelley gave me no verbal or written instructions regarding the use of the Oxytocin. He never mentioned that he would have to see my animals before prescribing the medication. Dr. Skelley did not tell me that Oxytocin was an Rx drug, but he did indicate on the invoice he gave me (SUMMER ST. RD. ANIMAL CLINIC Invoice #12310 dated 8/24/84) that the product was Rx, in the "DESCRIPTION CODE" box. I left the clinic at approx. 12:20pm.

Investigator (324)
STL-STA/Cedar Rapids Resident Post

Page 1 of 1 Pages

FORM FDA 464a (6/82) Previous edition may be used. C/R CONTINUATION SHEET

SAMPLE RECORD COPY 1

1. COLLECTOR (Print or type name)	2. DISTRICT	3. C/R NO.	4. DATE COLLECTED
	STL	85-345-237	10/16/84

5. REMARKS

#s 23,27 Upon entering this clinic I was greeted by an approx. 5'4", thin,28 yr old female employee who asked if she could help me. I told her I wanted a small bottle of Lutalyse. She acted as if she wasn't familiar with the product and asked what it was used for. I said that I didn't know, and that my stepdad had sent me in to get some. She asked the name. I responded - Jamieson - Tom Jamieson. She went to a large "power" file behind the counter area and tried to find a "folder" for Tom Jamieson. She asked if he had "bought" there before. I said that I thought so. She then went to the card file located to the left of the front counter area. She found a card for Tom Jamison Box 207, Burlington. I said that that was "him" and had the spelling corrected to Jamieson. I had a chance to glance at the card and noted that it listed as a single entry my previous purchase in 7/84 of Oxytocin (CR 84-495-711). She then went to a back area and I overheard her ask another female what Lutalyse was used for. I did not hear the response clearly but that second female called out to me - What kind of animals. I said that I didn't know. She then asked - Does he have horses. I said no. The first female then came forward with the sample which I purchased, paying cash. The second female also came forward and we struck up a conversation . She identified herself as a veterinarian. She was approx. 5'7", thin and 28 yr old. I then left the clinic. After driving off, I realized that I had not been given a receipt. I returned and was greeted by the first female. I asked for a receipt for "him". She made out the attached invoice #12420. In glancing at the counter I noticed what I thought was the card for Tom Jamieson, which had been updated to reflect the purchase of Lutalyse. I then left the premesis. At no time did they ask if I had a Vet prescription or was purchasing the product on the order of a Vet.

Attached: Dealer Invoice(Receipt) #12420 dtd 10-16-84
Seal dtd 10/16-29/84

FD FORM 464a (1/73) C/R CONTINUATION SHEET

SAMPLE RECORD COPY 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date JAN 23 1985

From Case Guidance Branch, HFV-236
Division of Compliance, CVM

Subject 85-345-299 "Oxytocin" Injection
RE: "IOWA VETERINARY STRATEGY" for Illegal Distribution of
Veterinary Prescription Drugs

To Chief, Case Guidance Branch
Division of Compliance
Center for Veterinary Medicine

Firm: Dr. William Cusick
214 First Street, SW
Dyersville, Iowa 52040

REGULATORY LETTER APPROVED

We concur with the district's recommendation charging 502(f)(1). The recommendation is in accordance with the "IOWA VETERINARY STRATEGY". It does not meet the minimum criteria of Compliance Program 7365.002 Illegal Distribution of Veterinary Prescription Drugs.

On 10/18/84, one veterinary prescription drug, Oxytocin Injection, (85-345-299) was purchased at the firm by a FDA Investigator without a prescription or other order from a licensed veterinarian. Oxytocin Injection is subject to regulation (21 CFR 522.1680).

It should be pointed out that a male employee (maybe a veterinarian) did ask the FDA Investigator if was a Federal Agent. When question was ignored, he stated that the firm was not supposed to sell the product to someone they didn't know. The female employee did ask about a prescription. When the FDA Investigator stated that didn't know, the male employee stated that he did not care about selling the Oxytocin. But, he did state that he did worry about "tranquilizers" because "kids" might try to use them on themselves. The male employee got the product for the investigator and the female employee made out the invoice and completed the transaction.

Stanton W Johnson
Stanton W. Johnson
Consumer Safety Officer

11-7-84
ORS

1. FLAG: CP7363.002-Do not strip label-Photocopy only
Complaint

2. TYPE SAMPLE:

3. SAMPLE NUMBER: 85-345-299

4. CF NO.:

5. JD-TA:

6. COUNTY:

7. DATE COLL: 10/18/84

8. PRODUCT CODE: 68FCP20

9. RESP FIRM: D

10. PROGRAM ASSIGN CODE: 1. 65002 2. 3.

11. HOURS: 1. 3 2. 3.

12. RELATED SPL: NA

13. PC: 2

14. COLL NO.: 203

15. SPLING DIST: STL

16. COLL DIST: STL

17. PRODUCT NAME AND IDENTIFICATION *(Quote pertinent labeling including firm name and address)*

Oxytocin injection in glass bottle labeled in part:"...OXYTOCIN,..CAUTION: Federal law restricts...NET CONTENTS: 30ml...EACH ml. CONTAINS: Oxytocin (synthetic) 20 USP units...TechAmerica Group, Inc. Elwood, KS 66024...3235D 8-85...".

18. REASON FOR COLLECTION *(Indicate analysis needed & document assignment. Include CP No. and/or Assignment No. if applicable.)*

Illegal distribution of vet Rx drugs. Photocopy labeling. Do not strip. Do not analyze.

19. MFG CODES *(Labels, pkg, shipping containers)*

3235D, [illegible] 8-85 [illegible] on bottle label

20. MANUFACTURER *(Name, address & ZIP)*: unknown

21. SHIPPER *(Name, address & ZIP)*: unknown

22. DEALER *(Name, address, ZIP & telephone)*

Dr. William Cusick
224 First St SW
Dyersville, Ia 520[illegible]
319-875-8393

23. SIZE OF LOT FROM WHICH SAMPLED: unknown-see remarks

24. EST VALUE: unknown

25. RECEIPT ISSUED: FD472 ☐ FD484 ☐ NONE XXX

26. DATE SHIPPED & DOC REF: unknown

27. DESCRIPTION OF SAMPLE AND METHOD OF COLLECTION *(Number and size of units, etc.)*

Sample was purchased OTC by this investigator as a person off the street. The sample consisted of 1 bottle of product described in #17 above. See Rmks.

28. HOW PREPARED

Bottle label identified as per #29. Bottle placed in bag and sealed 10/18-11/2/84. Seal broken 11/2/84 by this investigator and the CR was prepared. Sample placed in paper bag and sealed as per #30 with FD525 attached. (cont)

29. COLL IDENT ON PKG AND/OR LABEL: "85-345-299 10/18/84 GAL"

30. COLLECTOR'S IDENTIFICATION ON SEAL: "85-345-299 11/2/84 ..."

31. SAMPLE DELIVERED TO

US Postal Service
St. Louis, Mo

32. DATE DELIVERED: 11/5/84

33. LAB: KAN

34. LAB W/SPLIT SAMPLE: NA

35. ORIG C/R & RECORDS TO: STL

36. RCDS OBTAINED

a. INVOICE NO. AND DATE: Dealer #11539 dtd 10/18/84

b. SHIPPING RECORD *(B/L, F/B, Waybill, Affidavit, etc.)* NO. AND DATE: none

c. OTHER DOCUMENTS *(Affidavits from dealers, etc.)* SIGNER'S NAME AND DATE: none

37. REMARKS *(If additional space is needed, attach Form FD 464a, C/R Continuation Sheet)*

28. Bag placed into box with filler and shipped as per #s 31-33.

23,27 Upon entering I was greeted by a woman approx. 40 yr old, 5'6", 130 lbs who asked if she could help me. I said that I needed a small bottle of oxytocin. She asked my name. I said it was for Charlie Edwards. She then looked at a man standing to the right of the counter. He was approx. 55 yr old, 6', greying. He asked (cont)

38. CONSUMER COMPLAINT NO.: NA

39. AMT. $: 2.85
CRED. CD. ☐ C ☒ V ☐ B ☐

40. 704(a) SPL: YES ☐ NO ☒

41. COLLECTOR *(Typed name and signature)*:

FORM FDA 464 (3/71) PREV ED MAY BE USED.

COLLECTION REPORT

SAMPLE RECORD COPY 1

COLLECTOR (Print or type name)	2. DISTRICT STL	3. C/R NO. 83-345-299	4. DATE COLLECTE 10/18/84

5. REMARKS

23,27 cont - Are you a Federal Agent? I said - What? He laughed and said we're not supposed to sell this to someone we don't know. The woman then asked - Does he have a prescription? I said - I don't know. I continued - He just sent me in to get some. The man said that he doesn't care about selling - this (oxytocin). It's the "tranquilizers" I'm afraid of - kids might try to use them on themselves. He then produced the bottle of product from somewhere in the front area. I didn't see the shelf location/refrigerator area from where he got it. He placed it on the counter. The woman was making out the invoice at the time. I paid cash for the sample. I then left the firm.

Attached: Dealer Invoice# 11389 dtd 10/18/84.
Seal dtd 10/18-11/2/84

FD FORM 464a (1/73) C/R CONTINUATION SHEET

SAMPLE RECORD COPY 1

11-7-84
CDR

1. FLAG: CP 7365.002-Do Not strip label-Photocopy labeling

2. TYPE SAMPLE:

3. SAMPLE NUMBER: 85-345-295

4. CF NO.:

5. JD TA:

6. COUNTY:

7. DATE COLL: 10/17/84

8. PRODUCT CODE: 63PC120

9. RESP FIRM: 5

10. PROGRAM ASSIGN CODE: 1. 55002; 2.; 3.

11. HOURS: 1. 4; 2.; 3.

12. RELATED SPL: NA

13. PC: 2

14. COLL NO.: 203

15. SPLING DIST: STL

16. COLL DIST: STL

17. PRODUCT NAME AND IDENTIFICATION *(Quote pertinent labeling including firm name and address)*

Oxytocin injection in glass bottle labeled in part:"...100 ml...OXYTOCIN INJECTION...20 U.S.P. Units per ml...CAUTION: Federal law restricts...Manufactured For Anpro Pharmaceutical Arcadia, CA 91006...6432 4/86..."

18. REASON FOR COLLECTION *(Indicate analysis needed & document assignment. Include CP No. and/or Assignment No. if applicable.)*

Illegal Distribution of Vet Rx Drugs. Photocopy labeling. Do not Strip. Do not analyze.

19. MFG CODES *(Labels, pkg, shipping containers)*

6432 4/86
on bottle label

20. MANUFACTURER *(Name, address & ZIP)*: unknown

21. SHIPPER *(Name, address & ZIP)*: unknown

22. DEALER *(Name, address, ZIP & telephone)*

Brooklyn Veterinary Clinic
Brooklyn,Ia. 52211

(515) 522-7055

23. SIZE OF LOT FROM WHICH SAMPLED: unknown - See remarks

24. EST VALUE: unknown

25. RECEIPT ISSUED: FD473 ☐ FD484 ☐ NONE XXX

26. DATE SHIPPED & DOC REF: unknown

27. DESCRIPTION OF SAMPLE AND METHOD OF COLLECTION *(Number and size of units, etc.)*

Sample was purchased OTC by this investigator as a person off the street. The sample consisted of 1 bottle of product described in #17 above. See Remarks.

28. HOW PREPARED Bottle label identified as per #29. Bottle placed into bag and sealed 10/17-11/1/84. On 11/1/84 seal was broken by this investigator and CR was prepared. Sample then placed into paper bag and sealed as per #30 with FD525 attached. Bag

29. COLL IDENT ON PKG AND/OR LABEL: "85-345-295 10/17/84 GAL"

30. COLLECTOR'S IDENTIFICATION ON SEAL: "85-345-295 11/1/84 ..."

31. SAMPLE DELIVERED TO

US Postal Service
St. Louis, Mo.

32. DATE DELIVERED: 11/5/84

33. LAB: KAN

34. LAB W/SPLIT SAMPLE: NA

35. ORIG C/R & RECORDS TO: STL

36. RCDS OBTAINED

a. INVOICE NO. AND DATE: Dealer #0726 dtd 10/17/84

b. SHIPPING RECORD *(B/L, F/B, Waybill, Affidavit, etc.)* NO. AND DATE: none

c. OTHER DOCUMENTS *(Affidavits from dealer, etc.)* SIGNER'S NAME AND DATE: none

37. REMARKS *(If additional space is needed, attach Form FD 464a, C/R Continuation Sheet)*

28 placed into box with filler and shipped as per #s 31-33.
23,27 Upon entering the clinic I was greeted by a woman who was sitting behind the counter, approx 5'6",red/brown hair, 40 yr old, who asked if she could help me. I asked for oxytocin. She looked straight at me and said she didn't know me and asked my name. I said it was for my step dad - Frank Young from [illegible]nell. (cont)

38. CONSUMER COMPLAINT NO.: NA

39. AMT. $ 4.75

CRED. CD. ☐ C ☒ V ☐ S ☐

40. 704(a) SPL: YES ☐ NO ☒

41. COLLECTOR *(Typed name and signature)*:

FORM FDA 464 (5/78) PREV ED MAY BE USED. COLLECTION REPORT

1. COLLECTOR (Print or type name)	2. DISTRICT STL	3. C/R NO. 35-345-295	4. DATE COLLECTE 10/17/84

5. REMARKS

23,27 cont She said she would have to call her boss. She said that she wasn't supposed to sell that product to someone that she didn't know. She then placed a phone call. In talking into the phone she said that - there is a " " in here who want to buy some oxytocin, but I don't know . She paused then started laughing. When she hung up the phone I asked her what was so funny. She said that "HE" jokingly had asked her to ask me if I had an FDA badge. I said - what? She explained that the "Federal Drug Agency" sometimes sends peopl in to buy drugs. She added that Oxytocin wasn't a "narcotic" but that they weren't supposed to sell it to just anyone. I smiled. She had been standing at that time and went into a side room. She returned with the bottle of product. She wrote up a receipt and I paid cash. She then said - they come in, in all sorts of disguises. She then asked to see my driver's license. I showed my license to her (Illinois). She handed me the product and I began to leave. (Note- I was wearing) She asked me if I had a . I smiled again, then left. At no time did she ask me if I was purchasing the product on the order of a Vet or had a Vet Rx.

Attached: Dealer Invoice #6432 4/86
Seal dtd 10/17-11/1/84

FD FORM 464a (1/73)

C/R CONTINUATION SHEET

SAMPLE RECORD COPY

Mr. **Weiss**. Mr. Shane, as part of that undercover operation, didn't a female FDA undercover agent purchase, without a prescription, powerful drugs such as oxytocin and lutalyse from a number of establishments while in a pregnancy disguise?

Mr. **Shane**. Yes.

Mr. **Weiss**. And my understanding is that both of those drugs carry a warning that they should not be handled by pregnant women because they have the potential to cause abortions, is that correct?

Mr. **Shane**. That is correct, sir.

Mr. **Weiss**. Now, did the veterinary establishments selling these drugs realize that they were violating the law?

Mr. **Shane**. Yes; I think in most instances some of them even asked if we were FDA investigators and that it was illegal to sell the drugs. So they had knowledge that they were violating the law.

Also, in that instance, when they sold the drug to our female investigator, they did not warn her of the potential harm that could come to her from mishandling the drug.

Mr. **Weiss**. I assume that—well, let me ask it. Have you found that veterinary establishments often realize that they are violating the law when they sell prescription drugs for which no prescription has been written?

Mr. **Shane**. Yes; it seems to be basically that they will sell if they figure that they know you. I think probably now they are a little more concerned about making sales, but I still think if they figure they have done business with you, or they know you as a farmer who has animals, that they will make sales.

Mr. **Weiss**. So this is not a situation where veterinary establishments are making random or occasional mistakes, or where they do not understand that they are violating the law.

Mr. **Shane**. That is correct, sir.

Mr. **Weiss**. In an August 26, 1983, memorandum of a meeting on illegal sales with FDA's Orlando, FL, district, a Florida veterinary medical association representative observed that "up until now, veterinarians have had carte blanche in distributing veterinary prescription drugs."

[The memorandum referred to follows:]

To: ~~[illegible]~~
Dr Crandall
FYI

~~[illegible]~~ FYI ~~HFV-20~~ ~~[illegible]~~
Pls. Return for Files
JHL

Memorandum of Meeting

August 26, 1983

Attendees

Adam J. Trujillo, Director, Orlando District

Ernest L. Push, Supervisory CSI, ORL-DO

Terry C. Forrest, Supervisory CSI, ORL-DO

LeVar R. Lee, Compliance Officer, ORL-DO

Dr. S. F. Sundlof, Chairman, Drug Abuse and Misuse Committee Chairman, Florida Veterinary Medical Association

Richard Grant, Pharmaceutical Services Coordinator, Florida Department of Health and Rehabilitative Services

Dr. H. Larry Core, Executive Secretary, Florida Veterinary Medical Association

This meeting was held at the request of Adam J. Trujillo, Director, Orlando District, because of the concerns of the Food and Drug Administration (FDA), the State of Florida, and the FVMA in the area of illegal sales of veterinary prescription drugs in Florida.

Mr. Trujillo opened the meeting by explaining FDA's position and resources to deal with the illegal sales of veterinary prescription drugs. Mr. Trujillo mentioned that he had discussed the problem with Dr. Max Crandall, Director of the Bureau of Veterinary Medicine (BVM). Dr. Sundlof stated that he had been visiting BVM on another matter and had a discussion with Dr. Crandall concerning the illegal dispensing of prescription veterinary drugs in Florida and voiced his concerns. In his role as chairman of the committee on drug misuse and abuse of the Florida Veterinary Medical Association he was attempting to determine what the role of FDA is and what can be expected from FDA relating to this problem. At Mr. Trujillo's request, Ernest L. Push explained the current FDA program in the area of veterinary prescription drugs and explained the difficulty we have in the veterinary prescription drug area as opposed to human prescription drugs due to the lack of accountability requirements for veterinary prescription drugs. Mr Trujillo mentioned the difficulty we have in obtaining evidence by making undercover buys of veterinary prescription drugs and explained that we do not file cases without evidence that will win the case.

Mr. Grant stated that his agency had "cleaned up" twelve counties. When asked by Dr. Core what he meant by "cleaned up," Mr. Grant stated that his people had inspected feed and seed stores and similar facilities, under section 509 of the Florida regulations, dispensing veterinary prescription drugs and had stopped the sale of veterinary prescription drugs if they were not being dispensed by a firm and/or person licensed to dispense such drugs.

Mr. Trujillo explained the sanctions open to the FDA and the time factor and evidence necessary to take action. We do follow-up on complaints received and will continue to do so when they are sufficiently specific. Dr. Sundlof asked about the overlap in authority between FDA and Florida State. Mr. Grant said that he sees it as a coordinated effort. He said that he wants to rewrite the rules to include accountability so they will have to have records and files covering receipt and distribution of veterinary prescription drugs. Mr. Trujillo explained that we cannot require accountability. Mr. Grant stated that word is getting around regarding State action regarding illegal sales of veterinary prescription drugs. Inquiries are being received as to what the feed and seed stores can do to comply with the law.

Dr. Sundlof asked where the veterinarians fit in. Dr. Gore said that up until now, veterinarians have had carte blanche in distributing veterinary prescription drugs. Dr. Sundlof acknowledged that veterinarians sometimes handle drugs in an unprofessional manner, that veterinary prescription drugs find their way into human drug channels and that there is a need to curtail this distribution.

Dr. Gore mentioned the "impaired physician program" (use of drugs by veterinarians themselves) and said that he is overwhelmed by the flagrant misuse of drugs and biologics by veterinarians in the Midwest. Mr. Trujillo invited Dr. Sundlof and the FVMA to call ORL-DO if there is anything they think ORL-DO can do to help.

Dr. Sundlof stated that he is pleased that some actions are being taken and asked, "Where do we go from here?" Mr. Trujillo stated that we need specific information upon which to initiate action and that where it is best, we want to work jointly with the State. We also can assist in an educational approach by furnishing information, literature, and speakers. Dr. Gore stated that he feels the educational approach is an essential part of our overall effort. Dr. Sundlof stated that veterinarians plan an educational approach to both veterinarians and others involved in the illegal dispensing of veterinary precrition drugs.

Dr. Sundlof stated that he will report the results of this meeting and the cooperative attitude expressed by FDA and Mr. Grant to his committee at its next meeting.

La Var Lee
LaVar R. Lee
Compliance Officer
Orlando District

FR-4200/Gen Subject File

Adam Trujillo

c:
Max Crandall (HFV-200) ✓
-41/Kinslow
-4200/AJT
-4240/LRL/CB FILE
-4250/CCR
-8575/MIA-PP

Adam J. Trujillo
District Director
Orlando District

JT/LRL/dm/11-30-83

Mr. Weiss. Have you found that some veterinarians have engaged in unlawful prescription drug sales for a long time?

Mr. Shane. Yes. I think the practice has been going on for a long time. I think mainly it was the drug dealers, though, or out of the drugstores. I am not certain how recent the veterinarian distribution patterns are. I think that is a more recent phenomenon. It began—when they started to get into the retail drug business in conjunction with their veterinary practice.

Mr. Weiss. Have you found some veterinarians reluctant to comply with conditions imposed by the prescription legend because they've engaged in illegal sales with little or no Federal interference for many years?

Mr. Shane. I think that is probably true, sir.

Mr. Weiss. Consistent with the testimony you have already given today, the December 12, 1984, CVM memorandum mentioned previously states that this practice seems to be "driven by economics." Mr. Shane, is there anything about the current economics of the practice of veterinary medicine that, in your judgment, may contribute to the illegal sales problem?

Mr. Shane. Well, this would strictly be my own opinion, Mr. Chairman.

Mr. Weiss. Right.

Mr. Shane. I believe that probably there are a great number—too many veterinarians, in some respects, to support the need for their practice. I think in the State of Iowa, for example, there are 1,600 registered veterinarians. Even if you would take a number of those veterinarians and assign them other jobs, such as teaching and working for other firms, and left a thousand in the State to practice, that would be—there are 100 counties in the State of Iowa, so you would have 10 veterinarians in each county. And that far exceeds any supportable practice in the State of Iowa.

That, would be my own personal belief. I believe also that the farm economic situation is such that farmers are not calling on the veterinarian and trying to deal with nursing their own animals because it's expensive. And with the farm situation being such, a number of those farmers are not going to expend the money on a veterinarian if they can avoid it.

Mr. Weiss. Mr. Shane, one Iowa veterinarian engaged in illegal sales told FDA investigators that none of his "practices would change" as a result of their inspection because "he does not think he has done anything wrong. * * * He said that FDA will not change anything by this type of inspection, but will only drive the various practices underground."

[A report of FDA's inspection of this veterinarian follows:]

SUMMARY OF FINDINGS:

This inspection was done under Compliance Program 7365.002, Illegal Distribution of Veterinary Prescription Drugs. During this inspection the firm's policy and practices regarding the sale of prescription drugs was covered. The following undercover veterinary prescription drug buys have been made at this firm:

> two buys of Lutalyse which were submitted as Samples 85-325-898 and 84-325-989 and two buys of Oxytocin which were submitted as Samples 84-495-714 and 84-354-161. All four samples were collected at the firm between 7/24/84 and 10/15/84.

This inspection was made on the day of the last undercover buy (10-15-84). This inspection was made jointly by Investigators Davenport Resident Post has no inspectional history of this firm.

HISTORY OF BUSINESS:

This was apparently the first inspection of this firm. The firm operates as a typical farm community veterinary clinic. The firm is a professional corporation and was incorporated in 1977 or 1978. There are three veterinarians at the clinic: , President; , Vice-President and Secretary; and is the brother of who is President of ., doing business as Monticello Veterinary Clinic at Monticello, Iowa. did not know if the firm has a treasurer but he thought that also holds that office. is employed by the corporation but is not an officer. said that Mary Wilson is full-time office secretary and that Lois Kelting is part-time office secretary.

The bulk (80 to 90%) of the firm's business is within about 10 miles of the firm. There are some customers as far away as 20 miles.

PERSONS INTERVIEWED AND INDIVIDUAL RESPONSIBILITY:

Upon entering the firm we showed credentials and issued a Notice of Inspection to , DVM. He indicated that he did not have ultimate authority at the firm but said he was the most responsible person present at the time. We were then asked to wait until one of the other veterinarians arrived. arrived a short time later and he stayed with us for the remainder of the inspection. Practically all discussion after that was with When asked about responsibility, said he owns 51% of the business and has 51% of the say. signed an affidavit which discusses records accompanying the FDA drug buys and some general practices of the firm.

DOCTOR/PATIENT RELATIONSHIP:

No prescriptions are written for prescription drugs dispensed. A statement of the firm's policy regarding the sale of prescription drugs was included in the affidavit which was attached to Sample 85-325-898. A copy of that affidavit is attached to this report as Exhibit H. said that his firm has knowledge of conditions on all his clients' farms but not necessarily the specific animals being treated. He said he can prescribe medications based on that knowledge. All customers are reportedly repeat customers. Once a product has been prescribed the customer can then walk-in and buy that product again. The secretaries can also sell the product to a customer after the product has once been prescribed. We were not able to verify from the firm's records that a doctor/patient relationship is or is not made before prescribing veterinary drugs. In discussing this said that some of the records (invoices) show that farm visits were in fact made. However, said that while making a farm visit he could quite possibly sell prescription drugs to the farmer for animals not seen during the farm visit. On the other hand, the record might show a sale of prescription drugs when no farm visit was made. said the doctor/patient relationship for that particular client could have been established earlier, even possibly in a prior year. As stated earlier, said he has knowledge of the conditions on his clients' farms.

In discussing the doctor/patient relationship, we said the firm should have specific knowledge of the animals being treated and should not sell prescription drugs to just anyone who walks in, such as FDA investigators. indicated that they were suspicious of the FDA investigators when they came in to make undercover buys. In preparing the affidavit to document the shipments of the drugs bought by FDA investigators as undercover buys, we said that one other investigator (besides Investigators and) had been in to make buys. gave the impression that he knew exactly who the other investigator was. He said something to the effect "It was a woman. Wasn't it?" He indicated that the FDA investigators didn't look the part and said that we should wear bib overalls and grow beards. In response to why sales were made to FDA investigators, wanted it stated in the affidavit that instructions were given to the FDA investigators on the use of the drugs.

said that they feel that anybody who walks out the door with a drug will know how to use it. He asked who would buy drugs if they did not know how to use them anyway. That applies to Oxytocin, Lutalyse and SOW MIX (SOW MIX will be discussed later).

SELECTED DRUGS:

During this inspection, we obtained records documenting a receipt and sale of Oxytocin, Lutalyse, and Azimycin. As stated earlier, there is no way to document that an actual farm visit was made in connection with the sale of a specific drug.

At Exhibit A are nine invoices showing the firm's receipt of Azimycin. At Exhibit B are six invoices showing the firm's receipt of Oxytocin.

In obtaining these invoices we asked for records back to the first part of 1984. We were also furnished a copy of one invoice showing the firm's receipt of 24/30 ml. bottles of Lutalyse which was said to represent all the Lutalyse received in 1984. That invoice is submitted with Sample 84-325-898. The firm received Lutalyse from Sullivan Veterinary Clinic, Sullivan, IL on about 5-23-84. Undercover buys of Lutalyse and Oxytocin have been made at the firm (see "Summary of Findings").

At Exhibit C is a box label and insert for Azimycin. The label says the product is for cats, dogs and horses but not for horses intended for food. The firm mixes a product which they call SOW MIX. This product is sold with the firm's own label. A SOW MIX label is attached as part of Exhibit D, page 2. The SOW MIX contains 80 cc. Azimycin and 20 cc. Oxytocin. said the SOW MIX is prescribed for MMA (mastitis-metritis-Agalactia) syndrome in sows. said they sell about 30/100 cc. bottles of SOW MIX monthly. He also said his firm uses about 56/100 cc. bottles of Azimycin monthly for mixing SOW MIX which he said represents about 80% of their usage of Azimycin. In addition the firm has prescribed straight Azimycin for hogs and cattle.

We pointed out to that the Azimycin label says that the product is for non-food animals. He replied that any of the individual ingredients of Azimycin can be used in food animals and that it is only the combination that is not for food animals. He said as long as his firm makes their client's aware of the withdrawal period he does not feel that he is wronging anyone. said that he uses a 30-day withdrawal period for the SOW MIX. He said he would feel comfortable selling SOW MIX to someone he did not know, but he also said he would not sell Oxytocin or Lutalyse to just anybody.

The firm reportedly stopped using Chloramphenicol when the "Dear Doctor Letter" concerning Chloramphenicol was issued sometime last spring. We found no Chloramphenicol or DES during this inspection.

At Exhibit E are several invoices documenting sale of the following selected drugs from this firm to various clients.

Page 1, Exhibit E, documents SOW MIX (SOW MIX is also known as SOW MIX #2. There is also a product known as SOW MIX #1 which reportedly contains the single ingredient erythromycin).

Page 2, Exhibit E, documents Oxytocin and Lutalyse. The top invoice shows a charge for a farm call which demonstrates veterinarians visited the farm in conjunction with the sale of the drug. However, as described under the heading "Doctor/Patient Relationship", the visit to the farm may have been for reasons unrelated to the use of the drugs and the animals for which these drugs were prescribed may not have been seen.

Page 3, Exhibit E, documents the sale of SOW MIX, Oxytocin, and Lutalyse. Naquasone is also a prescription drug and also appears on page 3.

Page 4, Exhibit E, documents the sale of SOW MIX and Azimycin.

Page 5, Exhibit E, documents the sale of product referred to as S
#2 (which Investigator Iwen thinks is SOW MIX #2).

DRUG MIXING/FRONTROOM DISPLAY/MISCELLANEOUS:

at Exhibit D are labels which reportedly represent all the products that are routinely mixed at the firm. We were told that only one--SOW MIX--contains prescription drugs. As stated earlier, SOW MIX contains Azimycin and Oxytocin. The firm's two secretaries reportedly can mix any of these products. The secretaries can also sell the SOW MIX to walk-in customers whom they recognize as previously having the products prescribed to them. For mixing, formula cards are used. There is no central file for the formula cards; the formulas are taped to various cupboard doors. Photo 4 at Exhibit F shows two of these formula cards including the SOW MIX formula. There are no mixing records kept.

On the shelves in the frontroom retail display area we saw the following drugs bearing the prescription label:

Telmin Equine Wormer which contains 166.7 mg. Mebendazole. The product is in 12 gram packets. The firm name on the label is Pitman Moore, Inc., Washington Crossing, NJ.

Jet Biotic which contains per milliter 25 mg. Neomycin Sulfate, 2000 units Polymixin B Sulfate, 1.5 mg. Sodium Arsanilate and .02 mg. Spasmolysin.

Vet-A-Mix Diro-Form. Product in tablet form which contains 45 mg. Diethylcarbamazine per tablet.

MedTech Nemacide Chewable Tablets which contain 120 mg. Diethylcarbamazine per tablet. There is also a 180 mg. tablet of the same product.

1/8th ounce tubes of Neobacrimyl (Burns-Biotec, Omaha, NB) which contains 1% hydrocortisone acetate.

7.5 ml. tubes of Squibb Panalog Ointment with each ml. containing the following: Nystatin 100,000 units, Neomycin Sulfate 2.5 mg., Thiostrepton 2500 units, and Triamcinolone Acetonide 1 mg.

MedTech Neurosyn which contains 250 mg. Primidone per tablet.

Tech America Oxytocin with each ml. containing 20 USP units.

Naquasone Bolus with each bolus containing 200 mg. Trichlormethazide and 5 mg. Dexamethasone.

The foregoing products were commercially prepared products. Also on the shelves in the frontroom were three products which were manufactured and packaged at this firm. These products are: PIG MIX, SOW MIX, and SOW MIX #1. As stated earlier in this report, SOW MIX (also known as SOW MIX #2) contains two prescription drugs. Also as stated earlier in the report, the secretaries in the frontroom can sell any of the prescription items to anybody that walks in provided the secretary recognizes the customer as someone who has previously been prescribed the product.

In one of the backrooms, we saw several drums of Sulfathiazole Sodium which was apparently imported at some time in the past from the Netherlands. A photograph of the top lid of one of these drums is at photo 3, Exhibit F. At Exhibit G is a copy of the Bill of Lading showing from where the firm received this product, i.e., the agent is shown as Kuehne & Nagel Distribution Services, Inc., at 955 West Platt Blvd., Elk Grove Village, IL 60007. Also in the backroom we saw 15/25 lb. pails of Mer-A-Lite G which contains 312 grams per lb. of Sodium Sulfathiazole. We were told that Sodium Sulfathiazole is used primarily in treating respiratory infections in swine.

At Exhibit F are also included the following photos:

> Photo #1 shows Oxytocin on the shelf in the firm's frontroom retail display area and Photo #2 shows SOW MIX and SOW MIX #1 on a shelf in the firm's frontroom retail display area.

DISCUSSION:

We asked if any of the practices at his firm would change as a result of this inspection. He said that no practices would change. He said he would sell to another unknown individual because he does not think he has done anything wrong. He said he doesn't feel that he is putting the nation at risk. He said he is responsible to the people in his area, that the farmers are hurting, and he can't let their pigs die. He said the FDA should be looking at wholesale distributors before looking at firms such as his. He said that FDA will not change anything by this type of inspection but will only drive the various practices underground. He said that he feels that he is in compliance and that he is not adulterating the food chain.

During the inspection we explained Section 502(f)(1) of the FD&C Act in regard to misbranded drugs. We also explained the three basic penalty provisions of the FD&C Act, i.e., injunction, seizure, and prosecution. We said action could follow/ in the form of a letter or some type of correspondence requesting a reply. We explained that FDA takes a much harsher view of violations the second time around. We said it is entirely possible another FDA agent could come in and attempt to make another buy. We gave a copy of the FD&C Act to We briefly discussed the manufacture of drugs and the Drug Good Manufacturing Practices.

INVESTIGATOR
CEDAR RAPIDS RESIDENT POST

INVESTIGATOR
DAVENPORT RESIDENT POST

jai/cm
11-15-84

ADDENDUM

At Exhibit J are two pages of catalogs from two drug firms: Darby Drug Co., Inc., Rockville Centre, NY, and Henry Schein, Inc., Port Washington, NY. furnished these because they advertise Chloramphenicol.

At Exhibit I is a list of some of suppliers.

INVESTIGATOR
DAVENPORT RESIDENT POST
ST. LOUIS STATION

JAI/CM 11-27-84

Mr. WEISS. Mr. Shane, have you experienced or learned of similar responses from veterinarians to FDA's investigation of the illegal sales problem?

Mr. SHANE. We have had other veterinarians, in essence, respond that they wouldn't make any more sales to people they didn't know. I think that was sort of a common theme that ran through the veterinarians that we have talked to and the feedback we have received. They were very upset. They thought we picked on them in the State of Iowa. They figured we singled them out, made them look bad, and that has been the response from those people.

Mr. WEISS. Have you had discussions with any of these people as to what the public health consequences of their illegal behavior may be?

Mr. SHANE. Yes. We have sent them regulatory letters advising them of the illegal sales and the health consequences. As I pointed out, we had a large number of those veterinarians in the State of Iowa and specifically invited the 33 that were involved in the illegal sales, and laid down the law and expressed our public health concerns to those people. Dr. Crawford was there and addressed the group and expressed our policy that if it didn't stop, we intended to vigorously pursue regulatory action to make sure it stops.

Mr. WEISS. And yet you say that their response seems to be that you're picking on them, that you're singling them out for regulatory action. So that, there has been very little positive response from the perspective of morality or the public health consequences of their behavior. Is that correct?

Mr. SHANE. That would be correct, sir.

Mr. WEISS. Dr. Crawford, numerous documents in FDA files indicate that FDA staff believe far too few resources are available to stop this problem. In this connection, for example, I will place in the record a January 27, 1984, memorandum of a CVM field committee meeting, and a February 9, 1984, memorandum by Dr. William Bixler, CVM's Associate Director for Surveillance and Compliance.

[The memorandums referred to follow:]

MINUTES OF BVM FIELD COMMITTEE MEETING

January 27, 1984

BVM Overview; Extra-Label Use Policy - Dr. Lester Crawford

Dr. Crawford gave an overview of the Bureau's current focus and future direction. He emphasized that the Bureau will have a revitalized regulatory posture particularly with respect to important issues such as the new extra-label drug use policy. He explained the genesis of the policy and how it developed saying now that the policy has been articulated in its final form and communicated to the veterinary profession and agribusiness industry, it is important for instructions to be issued giving field guidance and to take some well-founded regulatory actions against flagrant abuses. Dr. Crawford also discussed the development of the aflatoxin program for the 1983 corn crop.

Field Concerns - Clifford Shane

Mr. Shane said that the Bureau's programs lack a sense of direction. With respect to the aflatoxin in corn program, for example, there has been no direction to the field offices regarding what FDA's reaction will be to violations of the announced procedures and permitted aflatoxin levels. There has been no direction on the extra-label drug use policy, which results in the field offices developing and submitting "trial balloon" cases. This is inefficient and ineffective. Lack of direction also exists with respect to the tissue residue and medicated feed compliance programs. The Illegal Rx Drug Distribution compliance program has inadequate resources and is not stopping the illegal practice. Mr. Shane suggested considering prosecutions rather than the more resource intensive injunctions against violations.

Long- and Short-Term Compliance Strategies - Dr. William Bixler

Mr. Shane suggested that BVM's program efforts should have both short-term and long-term objectives and strategies to provide a sense of direction. He asked for earlier communication and consultation with the field on new program initiatives. Mr. J. Paul Hile recommended use of the ORA Advisory Committee. Bureau Managers acknowledged that better communication, consultation, and planning were needed and would be forthcoming in the future.

Mr. Shane recommended, for example, that the extra-label use program could have been structured with a short term educational/informational approach followed by a long term strategy of regulatory actions. Because of resource restrictions and because we are in a precedent area, the effort should be focused. It was agreed to initially focus upon the use of chloramphenicol in feedlots and other large animal production units. Seizure of chloramphenicol in feedlots could be accomplished with minimal effort. Distributors should be tied into the effort - chloramphenicol should be the drug of choice in building illegal Rx distribution cases.

Illegal Use of Veterinary Rx Drugs - Dr. Andrew Beaulieu

There was general agreement with Mr. Shane's recommendation that this program needs to be reconsidered in view of the limited resources available and the perceived lack of impact of current regulatory activities in curbing illegal sales. Most agreed with his suggestion of restructuring the program toward taking prosecutions rather than injunctions against offenders as under the prior human Rx drug distribution program. Sufficient undercover buys would be made to establish the firm's pattern followed by a closeout inspection and prosecution recommendation. The suggestion will be given serious consideration by BVM.

Tissue Residue Follow-Up - Dr. Marvin Norcross/Dr. Myron Rosenberg

Dr. Rosenberg reported that listings of violations provided by FSIS to FDA field offices and to BVM differ significantly in content. He requested, and there was agreement for a trial period, for BVM to send to the field offices their computer printout to fill in the gaps in the field printouts and request that BVM's copy be updated with names from the field printouts. It was pointed out that in some instances where FSIS claimed they could not identify a producer, a phone call from BVM to the stockyard was successful in obtaining identity. It was suggested that BVM document this situation for transmittal to Mr. Hile for possible discussion with Dr. Houston at FSIS. The tissue residue compliance program is under revision and will be transmitted for field committee review after a regulatory strategy is agreed upon between BVM, ORA, and OGC.

Resource Exercise - Philip Frappaolo

Mr. Frappaolo discussed a document prepared for the purpose of justifying and requesting additional field resources for key program/problem areas, i.e., extra-label use; illegal sale of Rx drugs; tissue residues; medicated feeds; medicated premixes; and the sampling programs. A presentation will be made to Dr. Novitch.

Second Generation Medicated Feeds - Dr. George Graber

A restructured medicated feed compliance program is being developed for BVM and field committee clearance. An assignment has been issued over Mr. Hile's signature to the field offices under the OEI improvement program to obtain accurate listings of firms failing and passing directed inspections. Plans are being developed to withdraw FD-1800 approvals for firms failing inspection which produce medicated feeds containing Category II drugs. Reinspection will be required if in response to the NOOH and corresponding letters any firms either claim correction of GMP deficiencies or request a hearing. The field committee requested that the direction of the program be communicated to the field offices so they can communicate it to the states, as it will eventually impact upon state contracts.

Surveillance of the Animal Feed Industry - Dr. George Graber

The sampling programs, i.e., mycotoxins and chemical contaminants, are not statistically based because of resource restrictions. They do function more effectively as reactive programs. More resources are needed, especially for aflatoxin surveillance, and possibly other selective sampling programs.

Aflatoxin Update - Dr. George Graber/Dr. William Price

Mr. Shane reported that little corn is being shipped now, but it is expected that shipping will begin in March or April of corn released from storage under the PIK program. He asked whether BVM will support seizure of corn containing over 100 ppb aflatoxins. Dr. Graber advised that we would and that provided we cannot establish end use, seizure would be supportable on lots over 20 ppb.

Dr. Price reported that we have some preliminary results on mutagenicity testing of ammoniated aflatoxin-contaminated cottonseed meal, but no definitive conclusions. USDA completed safety testing of ammoniated aflatoxin-contaminated corn and will make the data available to FDA. They will not submit a food additive petition to FDA as postulated earlier. NCTR is working with USDA in the pathological and statistical analysis of the data. BVM will be reviewing the results. There were some problems turned up by a GLP inspection that need to be worked out. Also, some additional data may be needed.

Dr. Norcross said the human food safety requirements have not been met.

Veterinary Drug Production Quality Program - Dr. Andrew Beaulieu

The compliance program was restructured beginning in FY 1983 for the purpose of obtaining adequate base line data upon which to prioritize regulatory attention to the veterinary pharmaceutical industry. It is expected to take three years to inspect the 550 firm inventory to obtain the data. The intent is to split the program into smaller manageable programs. The current program requests completed GMP inspections and collection of all product labels. The field has been delinquent in collecting and submitting labels and will be requested again to fulfill that program requirement. Labels are being reviewed and assignments for regulatory follow-up will be issued as needed on significant violations.

Analytical Methodology - Dr. Marvin Norcross/Dr. Charlie Barnes

Analytical methods trial guidelines have been developed. A number of tissue residue analytical methods have been reviewed and validated under these guidelines. These include morantel tartrate, MGA, lasalocid, fenbendazole, ivermectin, and tiamulin. A method for albendazole is near completion and the trial of a method for levamisole is underway.

For regulatory purposes S&C will accept methods which have not been AOAC collaborated or validated provided adequate attributes are met. Tom Dols said that a guideline is being developed.

Veal Calf Task Force Meeting - Gary Stefan

Mr. Stefan reported on a meeting held January 26-27, 1984, by the Veal Calf Task Force which is part of the FSIS Residue Avoidance Program effort. At that meeting Dr. John Spaulding announced a more vigorous sampling and testing program for bob veal calves. The program is being implemented nationwide in an attempt to reduce the high rate of violative residues being detected in this class of animals. A copy is attached.

Communications with Field - Dr. William Bixler

The Bureau will improve communications and interaction with the field offices in its program initiatives. Mr. Shane asked for copies of BVM speeches addressing major policy issues, BVM Updates, etc., be sent to field offices. This will be done.

Attachment

February 9, 1984

Associate Director for Voluntary Compliance (Acting), BVM (HFV-200)

Field Committee Meeting

BVM Field Committee
Clifford Shane, Chairperson

As a result of our meeting on January 27, I thought it would be useful if we provided you with our perception of the various issues and what we are likely to do about them. Before I get into the details though, I judged the meeting to be excellent given the amount of time we had. I think it was a candid discussion of some very tough subjects which can only be dealt with as a team. As such, I intend to keep you heavily involved in these matters.

The following are the issues that emerged from our discussion listed in their approximate priority:

1. Chloramphenicol

   We are working on a comprehensive compliance strategy to deal with this problem. We will include the field committee in discussions of the strategy. This is a cross-cutting issue that impacts on three areas of concern: extra label use, tissue residues, and illegal sale of Rx vet drugs.

2. Illegal Sale of Rx Veterinary Drugs

   We also recognize this area as a significant problem with too few resources devoted to it. In the near future we will seek more time generally for BVM programs as we told you, some of which will go to this area. I also intend to spend some time examining the criteria that we use to recommend action to see if that criteria can be clarified (i.e., clearly state what constitutes flagrant behavior). We are also taking under advisement your recommendation to consider changing the preferred regulatory action from injunction to prosecution.

3. Tissue Residues

   This continues to be a difficult problem area. We are looking for better and more efficient ways to deal with the problem and develop better cases. Our current focus is the improvement of methodology and working more closely with USDA to include use of their analytical results in direct support of our regulatory actions. We also intend to fix any reporting problems that currently exist. The compliance program strategy is undergoing total revision and you will continue to be involved in that process.

4. Medicated Animal Feeds

Other than finalizing our regulation in this area which remains a difficult task, we continue to be faced with a 60% violative rate among the mills receiving directed inspections. Our intention there is to develop new guidance to deal credibly with these violative mills and to develop a strategy to withdraw FD-1800 approvals.

5. Aflatoxins

I think we have all learned a lot from our experiences in this area. We know that this will be a continuing and spotty problem. It will be important to have a continuing strategy to deal with it. Our hope is that the various state programs will go a long way towards controlling things when aflatoxin contamination is found. If a state program is not working, we will be prepared to take appropriate action. I would only ask that we consult with one another as to what that action ought to be.

6. Letters

There was concern expressed at our meeting about the proliferation of letters to advise firms of violations. I believe that there is no need to write more than one letter on any particular item. If we are prepared to take action then that letter ought to be a regulatory letter. If, however, the district decides that a Notice of Adverse Findings is indicated, it should not ordinarily be necessary to follow with an additional NAF or Regulatory letter. I believe this is consistent with the instructions in the Regulatory Procedures Manual.

In summary, the above are those priority items which will occupy much of our time over the next several months. I am attaching a more comprehensive account of the meeting prepared by Ed Ballitch so we do not lose sight of the other things discussed at the meeting. I intend to keep you up to date on all these subjects and provide as much information as I can on emerging Bureau policies. I am excited about my new assignment and the challenges that it presents and look forward to working with the field committee in meeting these challenges.

William B. Bixler, V.M.D.

Attachment

cc:

HFC-1	(Mr. Hile)	HFV-201	(Mr. Dykstra)
HFO-2	(Mr. Ottes)	HFV-210	(Dr. Beaulieu)
HFC-20	(Mr. Shumate)	HFV-220	(Dr. Graber)
GCF-1	(Mr. Levine)	HFV-230	(Mr. Ballitch)
HFV-1	(Dr. Crawford)	HFV-232	(Mr. Frappaolo)
HFV-2	(Dr. Guest)	HFV-300	(Dr. Norcross)
HFV-100	(Dr. Baldwin)	HFV-400	(Dr. Crandall)
HFV-200	(Dr. Bixler)	HFV-500	(Dr. Teske)

All Field Committee Members, Region Directors, and District Directors

2/13

GDykstra:pgk 2/8/84

Mr. **Weiss.** How many person-years are currently being allocated by the Food and Drug Administration to combating the illegal sale of prescription drugs?

Dr. **Crawford.** Well, virtually all of our field resources are at the present time, Mr. Chairman. As I mentioned earlier, that total number is about 175 person-years.

Mr. **Weiss.** And those are people who are dealing with prescription drugs being illegally dispensed without a prescription or order from a licensed veterinarian?

Dr. **Crawford.** Every and all aspects of the illegal drug distribution problem, including that, Mr. Chairman.

Mr. **Weiss.** Mr. Shane, what would your response be to that question?

Mr. **Shane.** My response is that we are carrying out all the programs for CVM, and that includes the requirements to make inspections every 2 years of all the drug manufacturers and following up on residue problems that are reported by USDA. So that 175 goes to a number of activities within the Center. As much as possible, we are dedicating as much time as we can, in addition, to see if we can spare people from other program areas to deal with this problem. So it covers the whole gauntlet of CVM programs. That 175 has a lot of responsibility out there.

Mr. **Weiss.** Right. And you have already indicated that there are these special undercover investigations that take place. You cited the one in Iowa and you say there are some ongoing. But beyond these special projects, on an ongoing routine basis, what level of resources are being allocated to combating the illegal sale of prescription drugs?

Mr. **Shane.** I could only speak for my region. And at the present time, I think we have about five to six people working full time in this area, but that will not be on a continuing basis. When we conclude these investigations then we will have to see what happens, but, right now, that is what we have committed to the program.

Mr. **Weiss.** How many regions are there in total, Dr. Crawford?

Dr. **Crawford.** Ten.

Mr. **Weiss.** Are the resources that you have committed, Dr. Crawford, sufficient to overcome this problem?

Dr. **Crawford.** Speaking region by region, what we are trying to do is concentrate them in the regions, Mr. Chairman, where there are problems and, also, where there are a lot of livestock. We have done the same thing we are doing in Iowa, essentially, in New York and in Puerto Rico. And as Mr. Shane has indicated, we have others set up.

We have asked for more field resources. We have asked for 19 percent more. And we believe that we need that in order to deal with this problem. As Mr. Shane indicated, and I think quite correctly, the illegal drug distribution problem, although not a completely recent thing, has gotten worse in recent years. So we need more resources in order to deal with it.

Let me indicate one of the ways we came up with that 19 percent, and that is because the field has been cooperative in trying to deal with the veterinary drug problem and have consistently overburned—by that, we mean borrowed from other programs within FDA in order to deal with the veterinary drug problem—to the tune of 15 to 20 percent over the last 2 to 3 years. And so we cannot keep borrowing from other programs; we need to reassign some of these.

Mr. **Weiss**. Mr. Shane, to your knowledge, has FDA ever prosecuted a veterinarian for illegally selling veterinary prescription drugs?

Mr. **Shane**. I cannot speak on a national basis. I am unfamiliar with any within my region. We have taken legal actions, injunctions against veterinarians, basically those people who are involved in the drug distribution business, not the illegal sale business.

Mr. **Weiss**. Dr. Crawford?

Dr. **Crawford**. We have some pending cases involving veterinarians, Mr. Chairman, and we have had some cases involving veterinarians in terms of distribution of nonprescription drugs, drugs of other sorts, including the drug DES. But in terms of prosecutions prior to the recent time or illegal actions, it is a recent phenomenon and except for those that are currently pending, I think the answer to your question is no; I don't think we have had these kind of actions since before 1982 or 1983, which underscores, I think, the fact that it is either recent or it has gotten worse during the past few years.

Mr. **Weiss**. Dr. Crawford, I understand that you believe that illegal veterinary drug distribution can present a greater public health threat than illegal distribution of human drugs?

Dr. **Crawford**. I do.

Mr. **Weiss**. Expand on that point.

Dr. **Crawford**. The record for that, Mr. Chairman, is that with human drugs the persons that are using them, for the most part, either consult with their pharmacist or with their physician, and, also, they are labeled in such a way that you can read what the drug is and what the hazards are which are associated with its long-term and short-term use. With respect to an animal drug residue that may be appearing in the meat, milk, or eggs of the American food supply over a long period of time, or even over a short period of time, since such residues are illegal, it is axiomatic that the meat isn't labeled, "This contains a drug"—say, for instance, chloramphenicol. And so the risk that is inherent there is not known. It also is known that most of these drugs are absorbable by the oral route; in other words, if you eat the meat, you can have the drug distributed throughout your body. And so a big error in animal drug residues that would be nationwide in scope could pose a greater problem for this reason and, also for the other apparent reason. And that is, a human drug is generally taken by one or two people within a community. If you've got a veterinary drug residue that occurs in the meat supply of the community, everyone there that eats that particular type of meat will be exposed.

Mr. **Weiss**. Have you communicated these concerns to the Commissioner of FDA and the Secretary of HHS?

Dr. **Crawford**. Not to the Secretary, Mr. Chairman, but to the Commissioner of FDA. We have had a number of briefings for this Commissioner and for the immediate past Commissioner on this particular problem, in which we detailed such specific things, actually, as the chloramphenicol problem and some of these others that we have been discussing today.

Mr. WEISS. What is FDA's strategy at this point to stem this epidemic of illegal drug sales?

Dr. CRAWFORD. The present efforts are several-fold. The first thing we needed to do was to expose the problem, and I mentioned our 1983 initiative in which we gathered together in Chicago a number of different organizations involved in livestock agriculture. We also exposed the problem through the trade press and through the popular press, and we made appropriate presentations to scientific and professional bodies. And we made a large number of contacts with State organizations that are in charge of enforcing the same food and drug concerns that we are, in order to get them aware of the problem.

One of the most successful liaisons we have had has been with the National Association of Boards of Pharmacy and, secondarily, with the American Veterinary Medical Association.

But, literally, with all those groups that would be involved, we have gone to them to expose the problem,

The second thing we needed to do was to convince them that we meant business, that we would take legal actions and that we would do things like the Iowa initiative and the New York initiative and the Puerto Rican initiative in the future, and that they be prepared; and that any misuse of an animal drug is a violation of Federal law. And that is something that all persons engaged in livestock agriculture in the United States needed to understand. And they also needed to understand the strength of our convictions. I believe we have made that impact. And now what we need to do is, in order to consolidate the gains we have made, to have what could only be called a "mop up operation." We need more field forces in order to deal with that and we are busily engaged in the reallocation that is necessary to accomplish that.

We still need the liaison with responsible groups, and we do not hesitate, Mr. Chairman, to go to every member of a various profession or trade organization. As I mentioned earlier, we wrote letters to the 40,000 veterinarians in the United States on this problem. And I might add, we got a good response to that.

We also recently, in concert with Don Houston, who is head of Meat Inspection at USDA, wrote a letter to 114,000 swine producers. And he and I have also cut television tapes, et cetera, to get on the farm programs in order to heighten the awareness.

Now, let me hasten to point out that this isn't just waving the banner. We tell them about the problem; we tell them what resources we have to deal with the problem in terms of the law; and then we also are exposing those cases that we have actually made, including face-to-face interaction with the veterinarians in Iowa and, also, with the veterinarians and livestock producers in two other localities.

Mr. WEISS. Since 1972, several FDA reports and the GAO have consistently found that USDA attempts to monitor for only a fraction of the animal drugs that leave residues in edible products. Mr. Dols, first, would you give us your responsibilities and then tell us whether this picture has changed appreciably since you last wrote about this problem more than 5½ years ago?

Mr. DOLS. Yes; I am the supervisory chemist in the Division of Surveillance, now detailed on a research assignment in our Beltsville facility. My responsibilities in the last 10 years have been—within CVM—to look at and review the cases that the field operation would bring into the Center, where they're involved in the analytical methodology as well as any good manufacturing practices.

Mr. WEISS. Mr. Dols, would you pull the microphone just a little bit closer to yourself. It is not as sensitive as it ought to be.

Mr. DOLS. Yes.

In other words, it was my responsibility to supervise the group of chemists that would review the analytical aspects of the regulatory cases in CVM. And many of these cases involved the residue methods and a review of the residue methods that involved the development of evidence in a court of law, analytical evidence in a court of law involving drug residue cases.

Mr. WEISS. Please tell us what you found when you wrote about the problem of monitoring for animal drug residues in edible products more than 5 years ago, and whether the situation has changed since then.

Mr. DOLS. Do you mean back in 1972 or in 1979?

Mr. WEISS. In 1979.

Mr. DOLS. In 1979, I wrote an update of the Johnson Memorandum of 1972, and I found at that point that there were only seven methods that I had, in reviewing the data, considered adequate in support or in enforcing the established tolerance for that particular drug. And in 1979 there were published and established tolerances for 81 residues. So that would be approximately 9 percent of the methods at that point in time were adequate in supporting the established tolerances. In other words, we had 9 percent coverage, approximately.

Mr. WEISS. Nine-percent coverage?

Mr. DOLS. That is correct.

Mr. WEISS. And for the rest, there were insufficient methods and effectively no monitoring. Is that the idea?

Mr. DOLS. For the rest, there were inadequate methods to be able to support any valid monitoring at that point. Basically, in 1972, I found that none of the methods that we had approved were really adequate, and now we had increased this to at least 9 percent.

[Excerpts from Mr. Dols' Nov. 14, 1979, update of the 1972 Johnson memorandum follow:]

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Fred Degnan, GCF-1

DATE: NOV 14 1979

OFFICIAL USE ONLY

FROM : Thomas J. Dols, HFV-216

SUBJECT: Update of the September 27, 1972 Johnson Memorandum

SUMMARY

Since publication of the Johnson memorandum in 1972, FDA has currently available only seven drug residue methods that are adequate to support regulatory action under the FD&C act. Part of the problem has been the agency's failure to define analytical criteria for residue methods in terms of the actual regulatory purpose of the methods; and publication of a proposed regulation that requires methods that identify as well as quantitate the drug residue. This can easily be resolved by discussion between the appropriate BF and BVM chemists.

Even though adequate residue methods are the key to any viable compliance program, they are not the only problems. We still have problems with USDA's sample integrity documentation, USDA's sample handling and the reliability and accuracy of USDA's residue results.

I recommend that BF and BVM prioritize the drug residues as to toxicity and potential for abuse; FDA make available the appropriate analytical criteria as well as publish a proposed FR regulation revising section 514.1(b)(7), FDA initiate dialogue with USDA concerning our regulatory needs (including the feasibility of joint effort in developing adequate screening procedures); FDA support and fund method development efforts within the agency to correct the deficiencies of the currently inadequate residue methods for the drug residues we wish to regulate; and that FDA investigate the feasibility of developing and validating multi-residue regulatory and screening procedures. In essence, the Agency lacks at this time a comprehensive compliance strategy on drug residues that would give assurance to the American public that the meat supply is not periodically being contaminated with unsafe drug residues from veterinary drugs the Agency has permitted to be used in food-producing animals.

Earlier this summer, Dr. Crawford assigned Mr. Degnan to chair a task force to develop some type of general guidance and criteria regarding the type of information that must be collected in order to support a prosecution or other regulatory action against a producer who consistently caused violative tissue residues in food producing animals. The results of this task force will aid BVM in writing this year's drug residue compliance program. A critical part of this task force is to determine the adequacy, reliability and sensitivity of the analytical methodology that is presently available for drug residue analysis which can subsequently be used as evidence in a court of law. Since the September 27, 1972 Johnson memorandum (given in Attachment 1) dealt with this same issue and its conclusions were verified by subsequent task forces, it is a relatively simple matter to determine and review the changes in residue methodology that have taken place since the Johnson memorandum was written using the same criteria for review; namely the type of suitability data needed by an expert witness to support, in a court of law, the adequacy of the residue methodology for its intended purpose. Where the residue methodology has not changed since 1972, the conclusions of the Johnson memorandum would still hold.

Section I of this report will list the changes in NADA approvals, established tolerances and revised residue methodology that have taken place since the Johnson memorandum was written. Section II lists the current pesticide residues that have established tolerances in meat. Section III lists the drug residues currently monitored by USDA. Section IV of this report will discuss the evolution of FDA policy in regard to the drug residue issue and the evolution of the analytical criteria used for approval of drug residue methodology since the Johnson memorandum. The revised residue methodology available since the Johnson Memorandum are reviewed in Part V. Part VI gives a discussion of the impact of the findings found in Part V on FDA's drug residue compliance program. Part VII gives my recommendations.

PART I - METHODOLOGY CHANGES SINCE THE JOHNSON MEMORANDUM

Since the conclusions of the Johnson memorandum have been verified by subsequent task forces, they still hold true for the residue methods that have not changed since 1972.

A number of changes have occurred in the lists and methods reviewed in the Johnson memorandum since September 27, 1972.

A. The following NADA approvals have been revoked:

1. Diethylstilbestrol
2. Testosterone
3. Reserpine
4. Nihydrazone
5. Racephinicol

B. The following NADA approvals have been added:

1. Ampicillin with a tolerance for negligible residues in tissue of swine and cattle and in milk.

2. Cephapirin with established tolerance in milk and tissue of dairy cattle.

3. Cloxacillin with a tolerance for negligible residues in milk and tissue of cattle.

4. Gentamicin Sulfate with a tolerance for negligible residues in tissue of turkeys.

5. Lasalocid Sodium with an established tolerance in tissue chickens.

6. Pyrantel Tartrate with established tolerances in tissues of swine.

7. Robenidine HCl with established tolerances in tissues of chickens.

8. Virginiamycin with a tolerance for negligible residues in tissues of swine.

C. The following established tolerances previously approved have been changed:

1. Bambermycin - the previously established tolerances have been eliminated as not needed for safe use of the drug.

2. Penicillin - the previous finite tolerances have been changed to zero tolerance (presumably defined by the sensitivity of the method).

3. Promazine HCl - drug was withdrawn from use in food producing animals and the previously established tolerance has been eliminated.

D. The following NADAs have been supplemented for revised residue methodology changes:

1. Carbadox
2. Ipronidazole
3. Melengestrol Acetate
4. Lincomycin
5. Dimetridazole
6. Furazolidone
7. Nitrofurazone
8. Nicarbazin
9. Penicillin
10. Bambermycin

E. For the following drug residues there is published methodology that is not part of the NADAs:

1. Diethylstilbestrol
2. Sulfa drug residues
3. Arsenicals

F. The following NADAs are the subject of proposed Notice of the Opportunity for a Hearing on the withdrawal of the NADA approval:

1. Low Level Antibiotics
2. Estradiol Benzoate and Estradiol Monopalmitate
3. Furazolidone and Nitrofurazone

G. In addition, the issue of the residue level the residue method for Melengestrol acetate is required to measure reliably has not yet been resolved within the agency.

As a source of adequate residue methods for compliance purposes by FDA, the AOAC, 12th Ed. with all of its current revisions, is still not very helpful. Of the tissue residue methods actually having an official final action in the AOAC, only the total Arsenic residue method is adequate for regulatory and compliance purposes by FDA. The AOAC residue methods for 3-amino-5-nitro-O-toluamide, Clopidol, Decoquinate, Ethoxyquin, Nalidixic acid and Zoalene are the same methods found inadequate by the Johnson memorandum. The AOAC residue method for melengestrol acetate failed to include the mass spectroscopy confirmatory aspect of the GLC method. This will be discussed later in Part III of this report.

All of this distills down to new or revised residue methods potentially available since 1972 for the following drug residues:

Ampicillin
Arsenicals
Bambermycin
Carbadox
Cephapirin
Cloxacillin
Diethylstilbestrol
Dimetridazole
Furazolidone
Gentamicin sulfate
Ipronidazole
Lasalocid Sodium
Levamisole
Melengestrol Acetate
Nicarbazin
Nitrofurazone
Penicillin
Pyrantel Tartrate
Robenidine HCl
Sulfa drug residues
Virginiamycin
Zeranol

These residue methods will be reviewed in Part V of this report.

PART II - LIST OF PESTICIDE RESIDUES THAT HAVE TOLERANCES OR ACTION GUIDE LEVELS [illegible] IN VARIOUS MEATS

The Johnson memorandum discussed the pesticide residues in animal tissues by category rather than by individual pesticide entities.

As taken from the Pesticide News Guide the current pesticide residues that have established tolerances or action guide levels in various animal tissues are given below.

A. Current pesticide residues that have established tolerances or action guide levels in meat, fat or meat by-products of cattle:

Heptachlor and Heptachlor Epoxide (a)
Duiron
Acephate
Chlorobenzilate
Malathion
Methoxychlor
Chlordane(a)
Piperonyl Butoxide(b)
Pyrethrins(b)
Endrin(a)
Lindane
Aldrin(a)
Dieldrin(a)
Toxaphene
Perthane
BHC
2,4D
Dipropyldsocinchomeronate(b)
Plictran
DDT
Dalapon
Diazinon(a)
Azinphosmethyl
carbophenothion
Carbaryl(a)
Dioxathion
Diodine
Ethion
Tetradifon
Ronnel
Endosulfan
Linuron
Coumaphos
Diphenylamine
Trichlorfon(b)
Dimethoate(b)

Paraquot(b)
Phorate(b)
Terbacil
Propachlor(b)
Simazine(b)
Simazine(b)
Fenthion
Naled
Atrazine(b)
Nitrofen(b)
Diphenamid(b)
Famphor
Fensulfothion
Dichlorvos(b)
thiabendazole
Daminozide
Alachlor(b)
Mirex(b)
Gardona
Carbofuran
Chloroneb
Propargite(b)
Imidan
Phosalone
Aldicarb
DEF(b)
Propanil(b)
Chlorbromuron(b)
Ciodrin
Chlordimeform
Picloram
Benomyl
Ruelene
Carboxin
Cacodylic Acid
Pronamide(b)
CIPC(c)
IPC(c)
N-octylbicycloheptenedicarboximide(c)
Phenothiazine(c)
Sec-Butylamine
Supona
Bromoxynil(n)
Dialifor(b)
Oxydemeton Methyl
Metribuzin
Potassium Arsenite
Sodium Arsenite
Oxythioquinox(b)
MCPA(b)
Chlorpyrifos
Ethofumesate

Oxadiazon(b)
Profluralin(b)
Nitrapyrin(b)
Bentazon
Methoprene
MGK-264
Difenzoquat
Merafos
Pydrin(a)
Permethrin(a)
Profenofos(a)

Note (a) - administrative guideline
Note (b) - negligible tolerance
Note (c) - interim tolerance

B. Current pesticide residues that have established tolerances or action guide levels in meat, fat or meat by-products of swine.

Heptachlor and Heptachlor Epoxide(a)
Diviron
Acephate
Malathion
Methoxychlor
Chlordane(a)
Piperonyl Butoxide(b)
Pyrethrins(b)
Endrin(a)
Lindane
Aldrin(a)
Dieldrin(a)
Toxaphene
BHC(a)
2,4D
Dipropyl isocinchomeronate(b)
Plictran
DDT
Dalapon
Diazinon(a)
Carbophenothion
Carbaryl(a)
Dioxathion
Ethion
Ronnel
Endosulfan
Linwion
Coumaphos
Trichlorfon(b)
Dimethoate(b)
Paraquot(b)
Phorate(b)

Note (b) - negligible tolerance
Note (c) - interim tolerance

C. Current pesticide residues that have established tolerances or action guide levels in meat, fat or meat by-products of sheep and goats:

Heptachlor and Heptachlor Epoxide(a)
Diuron
Acephate
Chlorobenzilate(d)
Malathion
Methoxychlor
Chlordane(c)
Piperonyl Butoxide(b)
Pyrethrin(b)
Endrin(c)
Lindane
Aldrin(c)
Toxaphene
Perthane
BHC(c)
2,4D
Dipropyl Isocinchromeronate(b)
Plictran
DDT
Dalapon
Diazinon(c)
Azinphosmethyl
Carbophenothion
Carbaryl(c)
Dioxathion
Dodine
Ethion
Tetradifon
Ronnel
Endosulfan
Linuron
Coumaphos
Diphenylamine
Trichlorfon(b)
Dimethoate(b)
Paraquat(b)
Phorate(b)
Terbacil
Propachlor(b)
Simazine(b)
Naled
Atrazine(b)
Nitrofen(b)
Diphenamid(b)
Fensulfothion

Phorate(b)
Terbacil
Propachlor(b)
Simazine(b)
Naled
Atrazine(b)
Nitrofen(b)
Diphenamid(b)
Fensulfothion
Dichlorvos(b)
thiabendazole
Daminozide
Alachlor(b)
Mirex(b)
Gardona
Carbofuran
Chloroneb
Propargite(b)
Imidan
Phosalone
Aldicarb
Propanil(b)
Chlorbromuron(b)
Ciodrin(b)
Chlordimeform
Picloram
Benomyl
Carboxin
Pronamide
CIPC(c)
IPC(c)
N-Octylbicycloheptenedicarboximide(c)
Supona
Bromoxynil(b)
Oxydemeton Methyl
Metribuzin
Oxythioquinox(b)
MCPA(b)
Chlorpyrifos
Ethofumesate
Oxadiazon(b)
Profluralin(b)
Nitrapyrin(b)
Bentazon
MGK-264
Difenzoquat
Merdafos
Pydrin(a)
Permethrin(a)
Profenofos(a)

Note (a) - administrative guideline

Dichlorvos(b)
Thiabendazole
Daminozide
Alachlor(b)
Mirex(b)
Gardona
Carbofuran
Chloroneb
Propargite(b)
Imidan
Phosalone
Aldicarb
DEF(b)
Propanil(b)
Chlorbomuron(b)
Ciodrin(b)
Chlordimeform
Picloram
Benomyl
Ruelene
Carboxin
Pronamide(b)
CIPC(c)
IPC(c)
N-Octylbicycloheprenedicarboxinide(c)
Bromoxynil(c)
Dialifor(b)
Oxydemeton Methyl
Metribuzin
Oxythioquinox(b)
MCPA(b)
Chlorpyrifos
Ethofumesate
Oxadiazon(b)
Profluralin(b)
Nitrapyrin(b)
Bentazon
MGK-264
Difenzoquat
Merdafos
Pydrin
Permethrin
Profenofos

Note (a) - Administrative guideline
Note (b) - Negligible tolerance
Note (c) - Interim tolerance
Note (d) - Tolerance for sheep only

D. Current pesticide residues that have established tolerances or action guide levels in meat, fat or meat by-products of poultry:

Chlorpyrifos
Profluralin[b]
Nitrapyrin[b]
Bentazon
Glyphosate
Difenzoquat
Merdafos
Permethrin[a]
Profenofos[a]

Note (a) - administrative guideline
Note (b) - negligible tolerance
Note (c) - interim tolerance

E. Current pesticide residues that have established tolerances or action guide levels in eggs:

Heptachlor and Heptachlor Epoxide[a]
Acephate
Malathion
Piperonyl Butoxide
Pyrethrins[b]
Endrin[a]
Lindane[a]
Aldrin[a]
Dieldrin[a]
BHC[a]
2,4D
DDT[a]
Dalapon
Nicotine Compounds
Carbaryl[c]
Ethion
Ronnel
Coumaphos
Dimethoate[b]
Paraquat[b]
Phorate[b]
Propachlor[b]
Simazine[b]
Naled
Atrazine[b]
Nitrofen[b]
Dichlorvos[b]
Daminozide
Alachlor[b]
Mirex[b]
Gardona
Propargite
Propanil[b]
Chlordimeform
Picloram

Heptachlor and Heptachlor Epoxide(a)
Diuron(a)
Acephate
Malathion
Methoxychlor(a)
Chlordane(a)
Piperonyl Butoxide
Pyrethrins
Endrin(a)
Lindane(a)
Aldrin(a)
Dieldrin(a)
toxaphene(a)
2,4D(a)
DDT(a)
Dalapon
Diazinon
Nicotine Compounds
Carbaryl
Dioxathion(a)
Ethion
Ronnel
Coumaphos
Dimethoate(b)
Paraquot(b)
Phorate(b)
Propachlor(b)
Simazine(b)
Simazine(b)
Fenthion
Naled
Atrazine(b)
Nitrofen(b)
Dichlorvos(b)
Daminozide
Alachlor(b)
Mirex(b)
Gardona
Propargite(b)
Propanil(b)
Chlorbromuron(b)
Chlordimeform
Picloram
Benomyl
Carboxin
Pronamide(b)
CIPC(c)
IPC(c)
Supona
Dialifor(b)
Metribuzin

Benomyl
Carboxin
Pronamide[(b)]
CIPC[(c)]
IPC[(c)]
Supona
Dialifor[(b)]
Metribuzin
Chlorpyrifos
Profuralin[(b)]
Bentazon
Merdofos

Note (a) - administrative guideline
Note (b) - negligible tolerance
Note (c) - interim tolerance

F. Current pesticide residues that have established tolerances or action guide levels in milk or milk fat:

Heptachlor and Heptachlor Epoxide
Acephate
Malathion[(b)]
Methoxychlor[(b)]
Piperonyl Butoxide[(b)]
Pyrethrins[(b)]
Endrin[(a)]
Lindane[(a)]
Aldrin[(a)]
Dieldrin[(a)]
Toxaphene[(c)]
Perthane
BHC[(b)]
2,4D
Dipropylisocinchomeronate[(b)]
Plictran[(b)]
DDT
Dalapon[(b)]
Azinphosmethyl[(b)]
Carbophenothion
Dioxathion
Dodine
Ethion[(b)]
tetradifon
Ronnel[(b)]
Endosulfan[(b)]
Coumaphos[(b)]
Diphenylamine
DBCP (Nemagon)[(a)]
Trichlorfon[(b)]
Dimethoate[(b)]
Paraquat[(b)]
Phorate[(b)]

Terbacil
Propachlor(b)
Simazine(b)
Fenthion(b)
Naled
Atrazine(b)
Nitrofen(b)
Dicamba(b)
Diphenamid(b)
Dichlorvos(b)
thiabendazole(b)
Daminozide(b)
Alachlor(b)
Mirex(b)
Gardona
Carbofuran
Chloroneb(b)
Propargite
Aldicarb
DEF(b)
Propanil(b)
Ciodrin(b)
Chlordimeform
Picloram
Benomyl
Carboxin
Pyrazon(b)
Pronamide(b)
CIPC(c)
IPC(c)
Sec-Butylamine
Supona(b)
Dialifor
Oxydemeton Methyl
metribuzin
Oxythioquinox(b)
MCPA(b)
Chlorpyrifos(b
Oxadiazon(b)
Profuralin(b)
Bentazon
Methoprene
MGK-264
Merdafos

Note (a) - administrative guideline
Note (b) - Negligible tolerance
Note (c) - interim tolerance

In preparing these lists, no effort was made to prioritize the residues as to prevalence of usage, toxicity, use conditions and probability of residue in animal tissue vs. unintentional contamination. These are certainly important considerations in development of any compliance program.

These lists, compared to the 13 pesticides currently being monitored by USDA in their tissue monitoring program, indicate a lack of effective compliance in this area. The cause is certainly lack of adequate multi-residue screening and confirmatory procedures available for the many tolerances established by EPA today. This problem could best be handled by the current group in the Associate Commissioner for Compliance's office who are developing long range compliance strategy for pesticide residues in raw agricultural commodities.

PART III - CURRENT USDA MONITORING PROGRAM (JAN. THROUGH MAR. 1979)

Type of tissues monitored include fat, liver, muscle, kidney and injection site.

Residue	Cattle	Calves	Sheep&Goats	Swine	Horses	Chickens	Turkeys	Ducks&Geese	Rabbits
Pesticides in fat$^{(1)}$	X	X	X	X	X	X	X	X	X
Antibiotics$^{(2)}$	X	X	X	X	X	X	X	X	X
DES in liver	X								
MGA in fat	X								
Metal ions$^{(3)}$		X	X		X	X		X	X
Sulfa drugs$^{(4)}$									
Clopidol in liver	X		X	X		X	X	X	X
Carbadox in liver				X					
Arsenic in liver and muscle				X		X	X		
Gentian Volet in liver				X			X		

Note (1) - Aldrin, BHC, Chlordane, Dieldrin, DDT, Endrin, Heptachlor, Lindane, Methoxychlor, Toxaphene, PCB, HCB, Mirex, Strobane and Nonachlor (underlined are chemical contaminants in the environment).

Note (2) - Microbiological screening profile includes quantitation for Penicillin, Streptomycin, Tetracycline, Erythromycin, Neomycin, Oxytetracycline, Chlortetracycline and unidentified microbial inhibitor. Monensin is not currently being monitored.

Note (3) - Copper, Zinc, Iron, Nickel, Cobalt, Manganese and Chromium.

Note (4) - Bratton-Marshal screening method with GLC follow up for presumptive positives identification claimed for sulfachlorpyridazine, sulfadimethoxine, sulfaethoxypridazine, sulfamethazine, sulfanitran, sulfaquinoxaline, sulfathiazole, sulfamerazine, sulfachlorpyrazine, sulfamethoxypridazine, sulfabromomethazine, sulfamethiazole, sulfapyridine and sulfanilamide.

In Part VI of this report, I will discuss the adequacy of this monitoring program in fulfilling FDA's needs.

PART IV - HISTORY OF FDA POLICY AND CRITERIA FOR REVIEW, SUBSEQUENT TO THE JOHNSON MEMORANDUM

To understand how and why certain changes in residue methodology have or have not been made since 1972, it is necessary to review the history of the actions that have taken place subsequent to the Johnson Memorandum.

Explicit in the Johnson Memorandum was the simple conclusion that FDA was approving drug residue methods submitted in NADAs for drugs administered to food producing animals, that were adequate for determining the original drug depletion curve under controlled conditions but lacked the necessary specificity when used on unknown tissue samples in support of legal action for enforcement of the established drug tolerances. In essence, FDA could not enforce the established tolerance by the legal remedies available to FDA because FDA lacks adequate regulatory residue methods that could be supported in a court of law.

The Johnson Memorandum did not evaluate all of the inadequacies of the approved residue methods. If a residue method was found to lack the necessary specificity needed to support a regulatory action in a court of law, the method was termed inadequate without further review.

In August 1973, the chemists assigned to the Holt Task Force on Drug Residues reassessed the same NADA residue methods reviewed in the Johnson memorandum using the same analytical criteria, namely the adequacy of the specificity of the various methods in identifying the residue of interest in an unknown tissue sample as evidence in a court of law. In all cases, the Holt Task Force confirmed the analytical findings of the Johnson Memorandum. In addition, the Holt Task Force recommended that the approved drugs having established tolerances, etc., be prioritized on the basis of usage, conditions of usage and relative toxicity. Cyclic review of the NADAs for conformity with our present standards (including the residue methods) could then be accomplished in accordance to such a prioritized list. The Task Force missed the point when it said that not all approved residue methods may not have to confirm the finding of the residue method as identity of the residue substance. If because of toxicological reasons etc. there is no reason to enforce an established tolerance, then the tolerance should eventually be reviewed and changed. Enforcement of the established tolerance is the reason for the residue method in the first place.

From the 12/29/75 Commissioner's Working Group on Animal Drugs, the following policy concepts regarding residue methods were summarized:

1. Approval of new animal drugs shall require the availability of the methods to identify residues of the specific substances of concern, qualitatively and quantitatively at the level of interest. The approach used for residue identification may employ one or more levels of testing methods capable of confirming the presence and amount of the substance in question.

2. Approval of animal drugs shall not be given if methods that can identify the presence and amount of those drugs in animal tissues at prescribed tolerance levels are not available.

3. A description of methods that may be used for identification of drug residues shall be published by the Agency in accordance with general policies governing public availability of methods, i.e., as regulations or guidelines.

4. The SOM regulation establishes policy and scientific requirements for methodology for animal drugs that are or may be carcinogens, including the extensive use of metabolic work-ups and Mantel-Bryan technique. This regulation provides an operational definition of the zero level for carcinogenic residues to implement the "DES-proviso" of the Act.

5. A sampling and analysis for tissue residues may be conducted in stages proceeding from screening to specific confirmatory analysis, depending on circumstances, e.g., whether substances are carcinogens or not. For carcinogens at ultra-low levels confirmatory testing is required.

6. Tolerances need not be set to the limits of available methodology if toxicologically acceptable higher levels are justifiable.

7. USDA and FDA will utilize all or part of official methods for tissue residue analysis to the extent necessary and sufficient for meeting its needs. USDA need not await confirmation by FDA of residue findings before proceeding with actions; samples will, however, continue to be submitted to FDA for testing and follow-up as appropriate.

8. Approval of NADAs will not be granted until residue methodology has been validated by FDA.

In the meantime the first Joint FSQS/FDA joint committee had been meeting on residue methodology since 1974. FDA members wanted to develop criteria for acceptable regulatory analytical methods while USDA wanted each method reviewed on its own merits. The issue was never resolved nor had the committee received any guidance on its mission from either of the two agencies. The committee then discussed the problems of various methods then being used by USDA. The committee set priorities on joint method evaluations and validation but the committee using its own resources failed to accomplish any significant improvement or validation of USDA's methods.

By February 2, 1976, BF had requested certain sponsors to develop confirmatory (undefined) tests for drug residues by incompleting submitted supplemental applications for significant expanded uses of the drug until such methods were accepted by FDA.

See Attachment 2 for a copy of Dr. Settepani's Feb. 2, 1976, memorandum on confirmatory tests. It turns out that list B & C in that memorandum refers to requested confirmatory test as the basis for incompleting a supplemental application for a new use with adequate methodology was submitted and approved. In most cases, the sponsor has subsequently failed to submit acceptable confirmatory tests or failed to gain approval for the new use of the drug. Part of the problem has been that the sponsors do not know what constitutes a confirmatory test or what would be approvable.

From the March 11, 1976 BVM/BF meeting on the update of implementation of the policy concepts affecting animal drug regulations (a copy of the minutes are in Attachment 3), it was decided that the analytical criteria are to be identified (assigned to Dr. Howard of BF) and Mr. Brigham of BVM and would draft the necessary revised regulations. This would include the policy that a method that must be capable of identifying as well as quantitating the drug residue.

From the minutes of this meeting it is very clear that BVM/BF understood (from Dr. Gardner) that 21 CFR 514.1(b)(7) was to be revised to include the requirement that the residue method must also identify the drug residue. To this day the revised regulation (as a proposal), has not been published in the FEDERAL REGISTER.

Attachment 4 gives a copy of Dr. Howard's April 6, 1976 memorandum on Confirmatory Techniques for Veterinary Drugs. It is not a rigorous discussion on confirmatory techniques nor can it be called a guideline in any sense of the word. It is a gathering of a number of miscellaneous thoughts on the matter of chemical identity of an analytical result as generated from the presently approved drug residue methods. He pointed out the difference between USDA and FDA's use of the analytical results. He discussed the non-specificity of GLC results and the fact that such results are only presumptive and not definitive for the identity of the residue. He indicated that FDA preferred that the confirmatory tests be performed on the same extract as that used in the determinative step, if possible. In actual fact it should be required if we are to obtain the type of evidence needed in a court of law. What Dr. Howard's memorandum failed to discuss directly was the type of analytical evidence needed in a court of law to support a regulatory action by FDA and the types of residue methods and supporting data that are needed by an expert witness called upon to testify to the adequacy of the methodology and analytical work performed in supporting the findings.

Attachment 5 gives a copy of the 6/9/76 draft Interim Policy Guideline for Screening Analytical Methods for Drug Residues and the 9/13/76 draft Interim Policy Guideline for Analytical Methodology for Non-Carcinogenic Drug Residues.

The 1976 screening guideline in essence says USDA will do its own thing in regard to analytical methods for monitoring drug residues. USDA may proceed with regulatory actions based on its own analytical findings without confirmation of the findings by FDA. USDA reported violative samples are subsequently subject to confirmation by FDA utilizing the approved regulatory methods. No mention is made as to what constitutes such approved regulatory methods and are they adequate for their intended purpose. It is also beyond me why USDA would want to take economic sanctions against a farmer based on analytical results that have not identified the drug residue in question and could in fact be due to substance(s) other than the drug. Need for quick assays never justifies compromising adequacy of the methods for their intended purpose. The use of screening methods can certainly be used if it can be shown that they do not generate unacceptable false negatives and that the results of screening methods only constitute the first stage in any regulatory scheme (presumptive evidence). The second stage must constitute analytical work that adequately confirms both the amount and identity of the residue.

The 1976 draft guideline on analytical methodology for non-carcinogenic drug residues discussed the acceptance criteria of a method as to its: description and data; reliability; accuracy and precision; specificity; sensitivity; practicability; confirmation procedures; and method validation. In actual fact, these discussions constitute their definitions of the attributes a regulatory method must meet. They do not give the actual acceptance criteria for each attribute that the method must meet.

In general, the definition of a regulatory method should have included explicitly the requirement of identity of the residue substance. The term reliability of a method is a layman's term. It failed to discuss the need for optimization of a method. Accuracy and precision are lumped together with the term accuracy as described in terms of recovery while precision is described by the word consistency. These are again layman's definitions of these two attributes. Recognized definitions of these two attributes should have been used. Accuracy is related to the true value which in this case is best measured by use of various levels of dosed tissue whose composition is known by separate definitive methods. Precision is related to the random error of the method. Confirmatory procedures should have been discussed under the attribute of specificity. It failed to discuss the recognized attributes of limit of detection and determination limit where actual measurement of control tissue is essential. From a regulatory point of view the key attribute that sponsors were not made aware of is the attribute of specificity as defined in terms of FDA's needs. This discussion should have been expanded.

Attachment 6 gives a copy of the July 14, 1978 briefing memorandum and August 8, 1978 report on the second FSQS/FDA Joint Task Force on Evaluation of Tissue Residue Methods. This Task Force indicated there are major problems that exist in the animal drug residue area which impact upon the effectiveness of the drug compliance program. It believes that the centralized control point for program direction should be within SF and FSQS. It raises the major question of do we want to operate on the brink (or beyond) of what can be practically and reliably achieved by the current analytical technology. This raises the feasibility issue of establishing low level tolerances for drug residues that may or may not be enforceable by practical analytical methods, at least from USDA's point of view. It reaffirmed the analytical conclusions of the Johnson memorandum in regard to lack of specificity in the residue methods and agreed with one of the recommendations in the Johnson memorandum, namely, that both agencies should make a commitment to the development of multiresidue analytical procedures. It also concluded that there is a definite need to assess the antibiotic area and develop policy with respect to the need for definitive criteria. It also believes that the present joint USDA/FDA committee on drug residue methods cannot be effective under current operating policies and lack of charge and support. So far the only validation work completed was on the DES residue method as modified by FDA.

Dr. Sphon in his article in JAOAC 61, 1247 (1978) (Attachment 7) has given an excellent discussion of some of the analytical criteria for mass spectroscopy as a confirmatory technique. This information could easily be incorporated into any final guideline for regulatory methods measuring residues. Evan Horning's, review article in JAOAC 61, 1232 (1978), on the various mass spectroscopy techniques available for analysis of ultra trace levels of an exogenous compound in a biological matrix is given in Attachment 8 as background and source material.

Attachment 9 gives a copy of the June 19, 1979 FSQS/FDA Work Group Report on the Assessment of Criteria Used in Evaluation of Microbiological Tests for Antibiotic Products. It recommends that the analytical criteria to be used for antibiotic residues should be the same as those prescribed by the current proposed SOM regulation. This will effectively eliminate microbiological methods as regulatory methods and relegate them to the function of screening methods. It further recommends that the microbiological tests along with suitable confirmatory procedures could be accepted as official methods if they can meet the total residue and SOM analytical criteria. The microbiological tests can be used for the analysis of antibiotic residues if the sponsor can conclusively demonstrate by total residue studies that the parent compound or its metabolites possessing microbiological activity can serve as an appropriate marker to monitor the total residue of toxicological concern. Such tests must meet the SOM analytical criteria with the exception of the L_m criteria. The information now being required by BF on antibiotics from which an assessment is made as to the appropriateness of the marker residue in the monitoring of the total residue of toxicological concern. In any case, the Work Group recommended the SOM criteria (excluding the L_m criteria) be used in order to have uniformity of analytical criteria for antibiotics for the three FDA bureaus involved, which is not the case now. What this Work Group failed to discuss is what confirmatory tests would be adequate in combination with the microbiological method as evidence in a court of law to identify the residue. Certainly there would have to be data showing that the other antibiotics will not interfere in the set of analytical procedures.

The July 2, 1979 Report on the Antibiotic Fermentation Product Committee chaired by Dr. Osterberg (given in Attachment 10) shows the difficulty of applying the proposed SOM concepts to metabolic studies of Mycelial Cake (Biomass) or crude bulk antibiotics. How do you identify the toxic components of toxicological concern when the composition of the biomass will change after approval, depending on the conditions of fermentation? While the metabolism study of pure standard may have little relationship to the actual biomass.

The April 17, 1979 GAO report on, "Problems in Preventing the Marketing of Raw Meat and Poultry Containing Potentially Harmful Residues," contends that public exposure to drug and pesticide residues in meat have been underestimated; that contaminated products are marketed; and USDA and EPA and FDA efforts have been inadequate to prevent future shipments of contaminated meat. This report should be read by anyone involved in the assessment and revision of our drug residue compliance program.

Probably in response to the GAO report, FDA has formed a new drug residue methodology Task Force that is currently just getting underway. Its present charge (given in Attachment 11) is to do an indepth review of the currently approved drug residue methods and determine their adequacy and uncover their deficiencies. The review will be equivalent to a cyclic review of all approved drug residue methods.

Attachment 12 gives a copy of the current October 24, 1979 draft Regulatory Assay Guidelines as written by BF for the general safety requirements of the Act. In essence, it incorporates the same analytical criteria as found in the proposed SOM regulations.

DISCUSSION

The discussion that has taken place since the Johnson memorandum on the analytical criteria needed for approval of a drug residue method has in general, failed to come to grips with the ultimate purpose and use of the residue method within FDA; namely, the generation of analytical evidence to support regulatory action in a court of law. In this context, the analytical criteria and data supporting the method should coincide with what an expert witness in the area of Analytical Chemistry will need to be able to testify as to the adequacy of the analytical work performed in support of the analytical findings as they relate to the identity of the drug residue and the limits of the uncertainty associated with the quantitative results. The expert witness in analytical chemistry will be making his/her assessment from the available data supporting the various attributes of the method and the quality control data accompanying the analytical worksheet.

The adequacy of the work performed on the tissue sample using various analytical techniques involving different chemical-physical characteristics of the drug substance to identify the drug residue at the exclusion of other substances will certainly have to be evaluated on a case-by-case basis.

As an FDA Chemist who has worked in this regulatory area, I believe that the use of the proposed SOM analytical criteria in guidelines as the basis for approval of the NADA residue methods, will not obtain the type and quality of data on the attributes of the method that will be needed by the expert witness testifying on the adequacy of the method in support of the analytical findings. In fact, the L_m value is meaningless because it embodies procedures that cannot be derived from any of the recognized and sound principles of analytical chemistry. The proposed SOM document failed to require the optimization data needed that would fulfill its definition of dependability. Its practicality requirements are too negative. USDA in its monitoring program will always modify methods and develop multiresidue methods to fulfill their own objectives. It is only hoped that the residue methods they use do not give an unacceptable rate of false negatives. These methods are geared for screening purposes only. It has been agreed that FDA will only consider these results as presumptive positive and before any regulatory action is initiated under the FD&C Act, FDA will have to confirm the identity and quantity of the residue using analytical methods that are defendable in a court of law. Therefore, it is only FDA laboratories that have need of the residue method approved in the NADA. FDA has always given time and effort to potentially violative samples that have been uncovered by a previous screening procedure.

What the SOM document should have stated is that one time definitive techniques and methods are not useful as regulatory residue methods. SOM implies the proper definition of an analytical method, namely it is a set of written instructions completely defining the procedure to be adopted by the analyst in order to obtain the required analytical residues; but they fail to fulfill the purpose of the regulatory residue method, namely enforcement of the established tolerance on unknown tissue samples (unknown as to what the animal was fed over its lifetime).

Data demonstrating the analytical function of a method is important information to have available for an expert witness. It should be derived using reference standard, spiked matrix as well as dosed tissue where there is available information on the best estimate of the "true value." For accuracy, the former curve is then compared to the latter to determine first linearity of the method and any matrix effects. This the SOM document fails to do.

The analytical performance characteristic of accuracy relates the agreement between the measured concentration and the "true value." It necessitates that you have some independent means of measuring or obtaining a best estimate of the "true value." The principle components of accuracy are: (1) random error (precision) and (2) systematic bias. The proposed SOM document failed to properly define the term accuracy. It confuses quality control techniques (used after the attributes of an analytical method have been proven) with accuracy. Quality control data can never replace the initial proof of an analytical method.

For determination of accuracy the SOM document relies on the average recovery of spike samples. A tissue residue method by the nature of its matrix must be assessed for a systematic bias by dosed tissue samples that have been assessed for best estimate of the true value using independent definitive methods (such as measurement of dosed tissue samples using an appropriately radiolabeled compound). The use of average spiked recovery values is a quality control technique unless one has an independent estimate of the true value and prior information that the matrix does not interfere in the measurement.

The acceptable limits given in the SOM document are arbitrary and too rigid for tissue residue analysis in the ppb level. It does not address the situation that gives a 50% loss or systematic bias but is reproducible. If this can be demonstrated, this would be very supportable in a court of law by an expert witness. The slope of the linear regression line in the calculation of the L_m value is really the recognized technique for determining the systematic bias. The deviation and shape of the deviation from normalcy (slope of 1.0) from the actual accuracy plot slope in terms of % is a measure of the systematic bias of the method. This system cannot be used by bioassay type procedures. Attempts should always be made to reduce this systematic bias but can be acceptable in a court of law if there is data available that show that it is reproducible and the matrix does not randomly interfere in the measurements. Otherwise the method is out of statistical control and not defined as an analytical method.

Precision is defined as the random uncertainty associated with the result at a specific concentration level. In other words, it is the degree of mutual agreement among individual measurements made under prescribed like conditions. This random error of a method has many components such as the error within samples, among samples, day to day variation and variation between laboratories. It is usually described by the standard deviation of the mean of a number of measurements (usually 20) involving the significant components of random error at a particular concentration. The SOM document does not require the measurement of the attribute of precision directly. The SOM document has included the acceptable criteria of precision in their calculation of the L_m value which now have been discredited for not being based on sound scientific principles. It is a known fact that precision of a method is not independent of the level being measured. Therefore precision must be calculated from data at the specific level of interest. The SOM document violates this principle by using the 99% confidence limits of the L_m plot (which is influenced by all of the data at the various levels) as its measure of precision.

To show that the method is under statistical control by having acceptable precision at the time the method is developed is one thing. For an expert witness testifying on the uncertainty associated with a specific result of that method, quality control data involving precision of the method in the hands of the analyst is still needed.

Specificity of a method is defined as the ability of an analytical method to determine solely the component it purports to measure. An interfering substance for an analytical method is one that causes systematic error or bias in an analytical result for at least one concentration of the determinand within the range of the method. All of this implies that the potential interfering substances of interest have been tested by the method. This data then will characterize the specificity of the analytical result. An important aspect of this aspect is to measure the interference of the sample matrix (without the determinand) and determine its reproducibility. For tissue samples, this means analyzing various control tissues (stored under stated conditions of sample handling for various periods of time). At least twenty control tissues per type of tissue should be analyzed.

The magnitude and variability of the reagent blank should also be determined when the method was developed using different lots of reagent. For ultra trace analysis, a reagent blank may be required with every run as a quality control measure.

In all blank measurements it is important to obtain the best estimate of the true base line of the instrumental response at the point used for quantitation. In the case of GLC and quantification of peaks near the solvent front vs. standard solutions, it is important to draw on the sample chromatogram for control tissue, the continuous function of the baseline from the solvent front to the plateau of the chromatogram as determined from an injection of the solvent. The blank measurement is not just the averaging of the pen wiggles at the point of interest.

The definition of specificity in the SOM document is meaningless. The use of the phrase "a smooth and continuing function," does not even require that the analytical function of the residue method be linear in the concentration range of interest. It failed to give guidance as to what kind of data would be used to determine the attribute of specificity and what potential interfering substances should be tested by the method. Tissue residue methods used for compliance purposes should at least be tested to determine if the other drugs approved for use on the same species and drugs in the same chemical category interfere in the method. This will at least partially characterize the analytical result. An analytical method that is subject to unknown and varying interfering substances is a method out of statistical control and subject to generation of false positive results.

By the very nature of the matrix involved, a tissue residue method cannot be tested for all of the potential interfering substances when the diet, exposure and metabolism of the target animal are unknown. Just the number of potential pesticide residues, environmental chemical contaminants and dietary factors gives an indication of the magnitude of the problem. Therefore the aliquot used in the final determinative step in the residue method should be subjected to other analytical techniques that involve different physical and chemical properties of the compound of interest. It is the preponderance of this evidence that identifies the analytical result as the drug residue in question. It is this preponderance of evidence as to the identity of the residue that an expert witness will testify to.

As previously discussed, the lower limit of reliable measurement found in the SOM document is meaningless as an attribute of a method because it embodies procedures that cannot be derived from any of the recognized and sound principles in analytical chemistry. What should have been discussed are the performance characteristics of detection limit and determination limit for an analytical method. Attachment 13 contains our written comments on the proposed SOM regulation that discuss the derivation of the attribute that Dr. Lloyd A. Currie at NBS has called the detection limit. From this, a determination limit can be calculated. Essential to the former attribute is the determination of the control tissue blank and its variation from actual data as previously discussed in this report. The Y-intercept of an accuracy plot (as done in the SOM document) cannot be used as the blank value and its standard deviation.

As will be discussed later in this report for DES, the determination limit of a residue method may be dependent on the interference given by the tissue matrix actually analyzed. If this interference is dependent on the efficiency of the clean up steps in the method, then control tissue may have to be analyzed along with the regulatory sample as part of the quality control for the method.

It can be surmised from the above discussion of method evaluation that many of these performance characteristics of a method are interrelated and dependent on each other. This means that there is a hierarchy in the stages of method development. Once a candidate method has been preliminarily evaluated and shown to be a potential method for the defined purpose, an analytical function is determined using reference standards. The blank measurement of various control tissues is assessed. If acceptable, an accuracy plot for fortified control tissue is constructed to approximate the systematic bias of the methods. If acceptable, an approximation of the precision of the method at various levels is determined. If acceptable, the critical steps of the method are optimized and the final attributes of the method are determined using (known) dosed tissue samples. The point of this discussion is to demonstrate why you must know the linearity of the method, its systematic bias including the blank and the results of potential interfering substances before you can interpret the attribute of precision which should only relate to the random error of the method.

CONCLUSIONS

It is clear from the discussions that have taken place within FDA since the Johnson Memorandum that the Agency has decided that the 21 CFR 514.1(b)(7) regulation should be revised to include identity of the residue as a requirement for residue methods that are to be used to enforce the established tolerance. I recommend that BVM consider the draft in Attachment 14 which only encompasses the change of policy of the Agency. Any proposed regulation such as this would have to be accompanied by availability of guidelines on the details of the analytical criteria involved. As I have previously shown the current draft guideline from BF is unacceptable in meeting the intended purpose of the residue methods. I see no reason why chemists from the two Bureaus involved cannot jointly develop guidelines that fulfill the needs of both Bureaus.

PART V - REVIEW OF THE METHODOLOGY CHANGES SINCE THE JOHNSON MEMORANDUM

The methodology changes listed in Part I of this report are reviewed here. The analytical criteria I will use was previously discussed in Part IV.

A. DIETHYLSTILBESTROL

There are two complete sets of residue methodology for DES in cattle tissue involving GLC and mass spectroscopy for confirmation. They are purported to be applicable for liver, kidney, muscle and fat tissues. Only liver tissue is now assayed by USDA. The original Eli Lilly & Co. procedures was modified by FDA. The latter has not been published in a scientific journal but was entered as evidence in the DES hearings. It was the subject of two FDA validation trials. Both sets of residue methods are found in Attachment 15.

1. DESCRIPTION OF METHODS

In the 1973 Eli Lilly GLC method an 80 g. sample is extracted with methanol and centrifuged. An aliquot equivalent to 50 g. tissue is evaporated to remove methanol and hydrolyzed overnight using B-glucuronidase. In the resulting sample, free DES is purified by alkaline liquid-liquid extraction and is reacted with dichloroacetyl chloride to form the cis and trans DES diester. The DES diester is measured by GLC using a 5% UCW-98 column and 63 Ni-ec detector against control tissue similarly treated and the free DES eluate fortified with the appropriate reference standard of cis-trans DES and esterified. The trans DES isomer is used for quantitation. A standard recovery is measured along with each run by assaying a fortified control tissue that has been carried through the entire procedure and compared to the compensatory

PART VI - DISCUSSION OF THE IMPACT OF THE FINDINGS IN PART V ON FDA'S DRUG RESIDUE COMPLIANCE PROGRAM

The conclusions of Part V of this report indicate that FDA currently has available only seven residue methods that are adequate to support regulatory action in a court of law. They involve the following drugs:

Diethylstilbestrol (withdrawn from the market as of Nov. 1, 1979)
Melengestrol Acetate
Carbadox
Cloxacillin
Lincomycin
Lasaloid
Arsenicals

Except for the arsenic assay, these methods involving expensive and complex procedures that will require extensive quality control (including the use of control tissue) to show that the method was performed properly.

The approved residue methods that were found inadequate as regulatory methods suffer from various deficiencies. USDA's colorimetric and GLC procedures for sulfa drug residues would be considered an example of a procedure that is totally deficient either separately or together as a regulatory method. As concluded by FDA's Task Force on sulfa drug residues they do not even serve as good screening procedures. The quantitative procedure for parent robenidine residues may be considered an example of an inappropriate method, if in fact the parent robenidine is expected to metabolize to substances that are not measured but turn out to be of toxicological concern. Some methods, such as for pyrantel and nicarbazin, may be adequate as quantitative procedures (after some additional work) but FDA would have to develop and validate adequate confirmatory procedures before adequate regulatory methods become available. Other methods like the bioautographic procedures for monensin, hygromycin B and bambermycin contain concepts that could be used by FDA to develop new procedures that become adequate regulatory methods.

One of the reasons why, after seven years, FDA has not been able to correct the methodology problems disclosed initially in the Johnson Memorandum has been the agency's failure to decide on what a regulatory method is and what analytical criteria must be met for approval of the residue method.

The SOM analytical criteria, that the agency was intending to rely upon, turned out to be inappropriate for the intended purpose of the methods, and in some cases embodied highly suspect and undocumented technical principles and concepts. In part IV of this report, I have previously discussed what our analytical needs are, in BVM, for supporting the analytical results as evidence in a court of law. As a follow-up to this report I am sure that BF and BVM can jointly write an appropriate agency guideline on the analytical criteria for drug residue methods.

Once an appropriate analytical guideline is agreed upon, BVM should have available, a draft FEDERAL REGISTER proposal to revise the 514.1(c)(7) section to require NADA sponsors to submit residue methods that are capable of identifying, as well as quantifying the drug residue. See Attachment 14 for a draft of such a regulation. Currently the sponsor of a new NADA is not on notice of our needs. Therefore we have approved residue methods that are not adequate as regulatory methods.

The need for multi-residue screening and regulatory methods, and how this interrelates to the approval of individual NADA regulatory methods will be discussed later in this section.

Adequate residue methods for both screening and compliance purposes are the key to any drug residue compliance program. Yet, lack of adequate methodology is not the only problem that must be overcome before we can design an effective compliance program.

This list of seven available regulatory methods in no way implies that they encompass the drug residues having the most toxicological significance to the safety of man or do they encompass the veterinary drugs expected to have the most potential for abuse. Such priority listings would have to be based on evaluation of the toxicity data in the various NADAs and previous results of USDA's National Residue Monitoring Program involving valid screening analytical procedures where the false negatives are at a minimum) and samples that represent the population of animals treated with the specific veterinary drug, in general.

Under the present FSQS/FDA Memo of Understanding, FDA is notified when violative residue findings are encountered in meat and poultry tissues under the FSQS National Residue Monitoring Program along with the necessary reports, documents and tissue samples involved. FDA or cooperating state officials will investigate to determine the cause of the residue and the culpability of any individual who may have acted (or failed to act) in such a way as to be responsible for the residue. The analytical residue methods used by USDA in their program are best described as screening procedures which generate analytical results to help identify potential violators but would not satisfy the statutory requirements for evidence in a court of laws. It is only hoped that their screening procedures are such that they do not have a high rate of false negatives. It is up to FDA to analyze the pre-screened presumptive violative tissue sample by valid regulatory methods that will satisfy the statutory requirements for evidence in a court of law.

Currently FDA can only defend analytically seven drug residues as evidence in a court of law without major method development efforts on the sample. We certainly can list these seven regulatory methods in the analytical section of FDA compliance program on drug residues. Yet it must be pointed out that this interim action will not correct the basic problems of the present compliance program.

The requirements of a regulatory method have already been discussed in Part IV of this report. They constitute:

1. Presenting evidence as to the amount of residue found along with the uncertainty associated with its measurement; and

2. a preponderence of evidence for the identity of the residue quantified.

Presenting anything less as analytical evidence in a court of law would require inspectional evidence that would have to be equivalent to a full confession from the person responsible for the residue. It would be a waste of government time and money to write a compliance program based on obtaining such a confession. Therefore, to have an effective compliance program it is essential that USDA have adequate screening methods and FDA have adequate regulatory methods for all priority drug residues.

At the present time, FDA compliance programs for drug residues could be revised to include more detailed instructions for the Inspectional Section to determine cause and culpability. This may help the Agency to go beyond the current information letter to the farmer. Since the type of current compliance program has been responsible for uncovering many cases of cross-contaminated feed as the potential cause of a drug residue, this compliance work should be strengthened. Again, the success of this compliance work has been limited by available regulatory methods for cross contaminated feed samples.

Even if FDA had adequate regulatory methods for all drug residues that have an established tolerance, FDA would still have to contend with USDA's sample handling and sample integrity problems.

Previous conferences between USDA and FDA have discussed this problem. It is well known that USDA's documentation of sample integrity is almost nonexistant. For example, they do not use any official seals on the sample container nor does the USDA Meat Inspector document how the sample was collected. Therefore, the USDA Meat Inspector would be asked to testify solely from memory on how the sample was collected. USDA Meat Inspectors have been known to have plant employees collect organ samples and list the carcass numbers. USDA needs to implement an effective system for documentation of the sample integrity.

In addition, many of the samples received in FSQS and FDA laboratories have arrived unfrozen and in some cases decomposed. Such improper sample handling in essence, destroys the evidence. When Dr. Fazio of BF visited FSQS Peoria Laboratory, he even found partially decomposed samples being analyzed in their monitoring program. The sample handling problem must be resolved if we are to have a viable compliance program.

The effectiveness of FDA's Compliance Program for drug residues can be no better than the quality of the analytical results being reported to FDA by FSQS from their screening procedures. If many of the analytical answers are wrong, many hours of FDA inspectional (or state officials') time will be wasted. When Dr. Fazio of BF visited the FSQS Peoria Laboratory for FDA's Sulfa Drug Task Force he found analytical methods had been modified without validation, methods had been performed improperly which would lead to questionable results, and analysis of samples that were partially decomposed. In general, he found the analysis was performed with very poor quality control.

From FDA's standpoint it is also important that the screening procedures used by FSQS meet the criteria of minimizing the occurrence of false negatives. FSQS' screening procedures have never been validated for this criteria and I highly suspect many of their procedures would fail this criteria when tested.

Without accurate analytical results from FSQS we will never know the extent of the drug residue problem nor will we be able to assure the public that the established tolerances are being enforced.

A true drug residue in market meat can be caused by the following situations:

1. Feeding of unmedicated feed cross contaminated with a drug.

2. The drug depletion studies in the NADA supporting the approved withdrawal time does not reflect the actual field conditions found when the drug is marketed commercially.

3. Failure to follow the direction for use on the drug label including failure to properly follow the stated withdrawal time.

Any effective compliance program should address these three causes of drug residues. The first item is already the subject of a number of agency task forces on surveillance of feed mills, revised Medicated Feed GMPs and such concepts as the Drug Carry-Over document. Inspectional follow-up on reported drug residues and the feed involved is certainly a part of the compliance effort in minimizing this cause.

Verifying the validity of an approved withdrawal period is best done shortly after the drug is approved. For most of the currently approved withdrawal periods, there is sufficient marketing experience to indicate that they are valid. But because of the conditions of use, the current husbandry practices, the time length of the depletion rate and the toxicological significance of the residue it may be prudent on the part of FDA to verify the withdrawal period of a recently approved NADA. In such cases, we may require USDA (as a condition of NADA approval) to conduct a statistically valid but limited tissue residue survey on the drug shortly after it is commercially marketed. To do this, USDA must have immediately available, a valid screening procedure.

The approved regulatory method would not be appropriate for USDA's use. At present FDA does not have a mechanism for obtaining such screening procedures. The solution to this problem may involve joint USDA/FDA effort in development of two sets of multi-residue methods. One set to be used for screening purposes and the other set to be used by FDA for regulatory purposes. As the NADA is approved, the government laboratories modify the multi-residue procedures to include the new drug residue.

The third cause of drug residues (misuse of the drug) can be further subdivided into two distinct situations.

1. Because of clinical need and experience, the drug might become used for an unapproved claim that changes the approved conditions of use and/or violates the withdrawal period on the label. If the unapproved use of the drug favorably affects the economics of the marketed animals, the misuse of the drug could be significant.

2. Without any real economic gain, the drug is misused through ignorance, etc. From experience this situation is only a very small percent of the total use of a drug. Even under the best surveillance program, it cannot be eliminated totally. Only education efforts by government and industry are effective in keeping this cause to a minimum.

The former situation (where economic gain is involved) can be an important cause of drug residues. To detect and prevent this cause of drug residues should be a primary aim of any drug residue surveillance program. The drugs that lend themselves to this type of misuse of the drug might be predicted from a review of original efficacy data in the NADA or subsequent studies or reports in the literature and annual records and reports for the NADA. This type of information should help set priorities for the drug residue monitoring program. If the information is not available, an effective monitoring program itself would disclose trends that define the problem when it exists. Again, without adequate residue methodology (both screening and regulatory procedures) we will not be effective in defining and preventing this cause of drug residues.

Other systems of compliance have been suggested to replace or augment USDA's and FDA's present compliance programs. One system would involve pre-mortum slaughter testing of tissue samples using a quick laser light scattering technique to detect drug residues. Any positive findings would then result in holding the slaughter house responsible for tagging the animals and holding the animals until the drug residues were depleted before allowing slaughter of the animals. Again the problem is available methodology adequate for this purpose. FDA/USDA is currently funding a contract for the development of such methodology. It is very unlikely that the techniques can be developed that will have adequate sensitivity, accuracy, reproducibility and partial specificity for a broad range of drug residues. Any analytical scheme that has a high rate of false positives and/or false negatives is useless for the intended purpose. In such a case it would be questioned if the procedure could be defined as an analytical method. Even if the systems were feasible, it would be many years before it could become a reality and would not eliminate the need for the present USDA tissue monitoring program. We would still need data to define our residue problems as well as check validity of the new system.

Another system would involve quick analysis at the slaughter house. Such an approach is the USDA STOP program on dairy cattle for antibiotic residues. It involves quick on-site microbiological analysis of a swab of the kidney tissue of the slaughtered animal. Eventually, positive results would be the basis for condemnation of the kidney and liver, and further testing of the muscle tissue. The validity of the STOP program would depend on its correlation with results from reference microbiological and chemical methods of known accuracy, precision, sensitivity and specificity. So far the STOP program has not passed this test. If the STOP program passes, it might be expanded to other species but it is unlikely that similar methods could be developed for the non-antibiotic residues.

Another system would expand USDA's self certification program involving private residue monitoring. At present USDA has entered into agreement with two large poultry producers to have the producers operate their own residue detection program under USDA supervision with USDA continuing to spot check the companies' products. So far, one company's monitoring program only includes pesticides and environmental contaminants. The other companies' monitoring program (for turkeys) includes chlorinated hydrocarbon pesticides, ipronidazole, penicillin and tetracycline. Again, adequate methodology is a limiting factor. If successful it could only involve the large producer. Therefore it would not eliminate the need for USDA's present monitoring program.

The key to any system that actually attempts to prevent animal herds found to contain illegal drug residues from entering the marketplace, would depend on the ability to tag the violative animals to prevent sale of the animals to auction houses and then diversion to other slaughter houses. As the April 17, 1979 GAO report, "Problems in Preventing the Marketing of Raw Meat and Poultry Containing Potentially Harmful Residues," pointed out, USDA does not presently have this power. The use of state officials (for cooperating states) or Congressional action may be needed in this area.

In any case, USDA's Tissue Monitoring Program (for surveillance) along with FDA's Compliance Program on Drug Residues (for follow-up action) are still needed now and in the forseeable future. The other systems really involve the problem of preventing the marketing of meat found to be contaminated with illegal drug residues. The present system does not directly affect this problem. It attempts to affect the overall reduction of future violators.

In the long run, the most efficient system for analysis of drug residues either for screening or regulatory purposes, is through a set of valid multi-residue procedures. Such methodology does not exist now. Nor does FDA presently require the sponsor to submit a valid screening procedure. At the present time we are at the mercy of independently developed drug residue methods submitted by the sponsor of an NADA as a requirement for approval of the drug. This creates a near impossible situation for DEN-DO, the FDA analyzing laboratory for drug residues. Once adequate regulatory methods become available for most of the approved drugs having an established tolerance, DEN-DO would have on hand a maze of equipment and reagents to contend with as well as maintain an ability to conduct a bewildering array of complex procedures with appropriate quality control. The cost of performing these regulatory methods would be very high.

A better and less expensive approach (in the long run) is the development and use of multi-residue methods. This is even more important for the screening procedures used in USDA's tissue residue monitoring program.

With the appropriate support and funding by the Agency, there is no reason why FDA could not group the prioritized drug residues (that are amendable to a common determinative step) and develop a common extraction and clean-up procedures for the various tissues. Such procedures would be developed to extract efficiently the largest number of drug residues in a group. With properly optimized clean-up procedures we could solve most of the matrix problems experienced by almost all of the present residue methods. Then the various determinative steps could be developed and optimized for the largest number of drug residues in each group. Various confirmatory procedures would be developed for the resulting eluate. The needed quality control procedures should be written into the methods. The final procedures would then be extensively validated. The developed extract, clean-up and determinative steps could then be modified and validated for separate use in multi-residue screening procedures. Once the regulatory and screening procedures are available, FDA, in a revised guideline, could put drug sponsors on notice that for any new drugs, we would expect them to develop residue methodology that are congruent with FDA's multi-residue procedures. Until such milti-residue methods become available, FDA, in the interim, will have to develop suitable residue methods that are presently deficient as regulatory methods (at least for the priority drug residues). We will still approve suitable individualized residue methods for new drugs.

The present philosophy within FDA, to depend upon the cyclic review system to correct the presently deficient residue methods for marketed drugs having established tolerances, does not solve our immediate analytical problem. The cyclic review system is really dealing with a different problem, i.e., is the drug residue still considered safe when assessed from toxicity data that conform to our present-day standards? In fact, I suspect that in some cases, new data might show that there is no need for some of the presently approved tolerances.

It will take years for the sponsor to generate the appropriate toxicity from which we can determine what the established tolerance should be and what substance (metabolite) should a new residue method be measuring. For the presently approved drugs we have established tolerances that are now legally enforceable. Our problem is that many of the presently approved residue methods are inadequate to perform this function. In some cases we cannot even determine if we have a residue problem.

Therefore, for those priority drug residues with established tolerances that we wish to regulate now, FDA has no other choice than to redevelop the approved residue methods in order to correct their deficiencies and validate the modified procedures. This is work that is in addition to any multi-residue research program that may be funded. To have a viable compliance program, FDA needs adequate residue methods now. We have basically wasted seven years after the analytical problem was identified. We cannot depend on the drug sponsors to correct these methods in a timely manner. In some cases, we have already asked and received confirmatory procedures from the sponsor which are presently inadequate as regulatory method.

Both FDA and USDA have current critical needs for more appropriate and valid screening procedures for priority residues along with their associated quality control procedures. Without such screening procedures we will never be able to define which residues are presenting a problem and muster our compliance efforts to help solve the defined problems. FDA and USDA must first agree on the analytical criteria required for such methodology. Until multi-residue screening methods become available, USDA and FDA may have to jointly fund the development of interim screening methods. Without valid USDA screening we can never have a viable compliance program.

Basically USDA, FSQS, FDA/BF and FDA/BVM are all dependent on each other for the overall regulation of drug residues in the meat supply, irrespective of separate functions and laws each perform and enforce. What is sorely needed is the development of comprehensive (overall) compliance strategy that will be effective in the interim and long run.

PART VII - RECOMMENDATIONS

(A) I recommend that BF and BVM prioritize the current drug residues (having established tolerances) for toxicological concern and potential for misuse respectively. Compliance efforts should then be concentrated on specific residues according to their priority on this list.

(B) I recommend that BF and BVM jointly develop appropriate analytical criteria for residue methods that satisfy the intended regulatory purpose of the methods. Such a guideline should be made available along with a proposed FR regulation revising Section 514.1(b)(7) to include the requirement that the residue method must identify as well as quantify the resulting drug residue.

(C) I recommend that FDA initiate dialogue with USDA concerning:

1. FDA's need for sample integrity documentation from USDA. A model system should be explored with USDA and implemented.

2. USDA's problem of improper storage and shipment of tissue samples; and what assurance we can have that it will be resolved.

3. The poor quality of the analytical work being performed in USDA's monitoring labortories and the lack of any effective quality control procedures. We should mutually agree on the steps to be taken to resolve this problem along with the appropriate follow-up action to assure ourselves that the steps taken are effective.

4. The analytical criteria that screening residue methods should meet to fulfill the needs of both FDA and USDA.

5. Possibilities of joint effort for development of appropriate screening methods that meet the agreed upon analytical criteria.

6. Specific drug residue surveys we need conducted by USDA.

If the problems stated above need to be verified, I suggest FDA gain permission to conduct an indepth inspection of USDA's monitoring labortories and supporting documents.

(D) I recommend that the cyclic review system proceed as planned. But we should recognize that it will not solve our immediate analytical needs.

(E) I recommend that the agency support and fund method development efforts within FDA to correct the deficiencies of the currently inadequate residue methods that are on the list of priority drug residues.

(F) I recommend that the agency investigate the feasibility of developing and validating multi-residue regulatory and screening procedures.

(G) I recommend that the Agency formulate a comprehensive (overall) compliance strategy that will be effective both in the interim and the long run.

Until recommendations (A), (B), (C), (E) and (G) are implemented, FDA does not have a viable compliance program.

Thomas J. Dols
Thomas J. Dols

cc: HFV-1 (Dr. Crawford)
HFV-9 (Dr. Guest)
HFV-200 (Mr. Brunk)
HFV-214 (Dr. Scarr)
TJDols:pck:11-9-79

Mr. **Weiss**. Would you say that the situation has changed appreciably since you last wrote about it in 1979?

Mr. **Dols**. It has not changed drastically. I have not updated the Johnson memorandum since 1979. If we look at the new drugs approved from 1979 to 1985, new residue methods are approved covering 10 established tolerances. If we made the assumption that they are adequate and if we include a multiresidue method that has been developed by the Government for the sulfa drugs, we would have adequate residue methods covering 25 of the established tolerances out of a total of 83. This would amount to about a 29-percent coverage of the established tolerances, as of today, making the assumption that the drugs approved since 1979 are adequate for enforcement purposes.

Mr. **Weiss**. Let me see if I understand what you are saying. As I understand it, of the 83 or so tolerance levels that have been set for animal drug residues, at best there are adequate methods for detecting such residues only in roughly 29 to 30 percent of the cases. Is that the idea?

Mr. **Dols**. That is correct.

Mr. **Weiss**. So that as to 70 percent of the cases, we have no way of determining how close we are coming to meeting the tolerance levels established for those residues. Is that correct?

Mr. **Dols**. That is correct. We would have no way of accurately determining this—even if we monitored with the present methods that we have, we would have no way of knowing what the true residue was in the case of 70 percent of the drug residues where adequate residue methodology is not available.

Mr. **Weiss**. I am about to use a number of chemical terms, and I apologize in advance for butchering some of them. Let me ask you, Mr. Dols, is USDA currently monitoring for residues of drugs such as the nitrofurans, dimetridazole, gentian violet, and thiabendazole, all of which have been found by FDA scientists to be demonstrated or suspect carcinogens?

Mr. **Dols**. As far as I know, in reading the USDA's annual report on their residue monitoring program for 1984 and 1985, the drugs that you mentioned are not covered within the 1984 plan and 1985 plan by USDA and therefore are not covered in their monitoring system today.

Mr. **Weiss**. They are not being monitored?

Mr. **Dols**. They are not.

Mr. **Weiss**. Even though they are demonstrated or highly suspect carcinogens?

Mr. **Dols**. That is my understanding.

Mr. **Weiss**. Dr. Crawford, if, as Mr. Dols states, USDA is capable of assuring the absence of violative residues for only a small portion of veterinary drugs used in food-producing animals, how could you say in that speech last month that we earlier referred to that we "are approaching a virtual zero residue violation rate in meat, milk, and eggs"?

Dr. **Crawford**. Well, obviously, as Mr. Dols has pointed out, we are not able to monitor for all the products that might be used. As he mentioned, in the mid-1970's, we had literally no methodologies or tests that reputable chemists in the American Association of Analytical Chemists agreed were sufficient for, say, legal action and, parenthetically, for monitoring. By this time, we made some progress. We have got about—I believe you said 29 percent, or something like that. And we would like to have, Mr. Chairman, methods for all of these products. And we have set up within the Beltsville Division of Veterinary Research an analytical methodology unit, whose purpose is to work on these methods. We also have set up, starting in 1980, a laboratory in our Denver Regional Office, whose job it is, also, to work on these methods. And we have contracted out method validation trials and also methods development, so that we have—and our goal was to have at least 50 percent of them by now. We have fallen short of that goal. We have got 29 percent. We are continuing to work.

Now, let me say one other thing. And that is, there are some of these substances where it may not be possible to develop a chemical method for. If that is the case, then we will have to take action to take the product off the market. And we have done that in the past and we are continuing to do that.

Mr. **Weiss**. I appreciate that. But, again, it seems to me that, given how far we are from even reaching 50-percent coverage, that you may not be doing anybody a favor by suggesting that we are approaching a virtual zero residue violation rate.

In 1978, the manufacturer of ipronidazole—a drug approved for use in turkeys—submitted a study to FDA showing that it induced mammary tumors in rats. On April 9, 1985, Dr. Settepani of CVM wrote that FDA scientists have "conclude[d] that this drug is a carcinogen."

[Dr. Settepani's April 9, 1985, memorandum follows:]

April 9, 1985

(Acting) Program Manager for Human Food Safety
(HFV-70)

Food Safety Issues Associated With Marketed Animal Drugs

Deputy Director, Center for Veterinary Medicine
(HFV-2)

On July 12, 198~~3~~4, at the Center's "go-away" for PMS Managers at Leesburg, Virginia, I devoted a part of my presentation to a discussion of marketed animal drugs that may no longer be shown to be safe as required by the Act. This memorandum responds to your request, made at the wrap-up session of the go-away, to forward my concerns in writing to your office.

The memorandum consists of two parts. The first section contains a short description of the human food safety issue associated with each of about a dozen marketed compounds. This is followed by a discussion of several actions that the Center might take to address the problems identified in the first section.

I have sprinkled both sections of my report rather liberally with suggestions and recommendations. For the most part, these recommendations have not benefited from in-depth discussions with others in or outside the Center. For this reason, I expect these recommendations to be considered as trial balloons designed to stimulate further discussion of the issues and not as edicts to be reduced to practice as quickly as possible.

Finally, although I am convinced that the Center should significantly increase the resources it allots to the identification and resolution of human food safety issues arising with already marketed drugs, I have tried to remove any statement that appears to criticize anyone for past or present failures in this area. For one thing, I do not believe any such criticism is either warranted or deserved. Nevertheless, should anyone take umbrage with any of the statements or recommendations below, they are inferring something in this report that is certainly not intended.

Section I THE PROBLEM DRUGS

1. NITROFURANS - CVM has, in my opinion, moved with alacrity in pursuing an action to withdraw approval of nitrofuran-containing animal drugs that are no longer demonstrated to be safe. My only concern with these drugs is that we should be thinking now about actions designed to avoid development of a situation with nitrofurans similar to that which occurred with DES after it was banned, should the Center prevail in its effort to withdraw approval of the nitrofurans. I am referring, of course, to the continued illegal use of DES in hundreds of thousands of cattle after its manufacture and use were banned in 1979. It may be premature at this time to try to engage drug companies and animal producer groups in a dialogue on what will occur if nitrofuran animal drugs are banned. Nevertheless, it is probably not too early for us to begin thinking about this eventuality. There is no analytical method available that could be used to insure the absence of residues of nitrofurans from meat, nor is one likely to be developed. Thus, we must rely on other approaches to insure that a prohibition, if one is imposed, will be followed.

Recommendation

I propose that the Center establish a team charged with establishing approaches - availability of alternative drugs, investigating potential stockpiling of the nitrofurans, etc., to make sure that the use of nitrofuran-containing animal drugs stops if and when it is decreed to stop by the Commissioner.

2. NITROIMIDAZOLES - Dimetridazole and ipronidazole are both approved for use in turkeys; they are both the subject of an application for approval in swine; and both drugs are demonstrated mutagens. Incomplete carcinogenicity testing results with dimetridazole led our scientists to conclude that the drug is at least a tumoragen. Evaluation of carcinogenicity testing results with ipronidazole led our scientists to conclude that this drug is a carcinogen. The human food safety unit, then at the Bureau of Foods, recommended in 1976 that investigational authorizations for dimetridazole in swine be terminated.

FDA's field units report that both of these drugs, but especially dimetridazole, are very widely used "off the label" by swine producers.

In my opinion, the same food safety concerns that led us to terminate investigational use of dimetridazole in swine nine years ago should compel us to take whatever regulatory action is necessary to prevent exposure of consumers to a potential risk of cancer from misuse of nitroimidazoles in this species, and also, for that matter, from their approved uses in turkeys.

Recommendation

A broad assignment should be sent to the appropriate FDA Districts to document the use of nitroimidazoles in swine. Assuming that this documentation is forthcoming, strong regulatory letters should be sent to the sponsors of these drugs telling them to take steps to stop the extra label use of their drugs in swine. Finally, sponsors should be given a rigid timetable for submission of data demonstrating conditions of safe use of their drugs in turkeys as a condition of their continued approval in this species.

3. CARBADOX - Carbadox was approved in 1972 for growth promotion and to control dysentary in swine despite the fact that we knew the compound was a genotoxic carcinogen and that the most sensitive method of analysis available for residues in pork failed, by a wide margin, to permit monitoring of the drug's label-recommended withdrawal period. Following its approval, carbadox came under a further cloud when the results of carcinogenicity testing revealed that the primary metabolite of the drug was a more potent carcinogen in rats than carbadox itself. Several countries, most recently the United Kingdom in a Notice dated 18 July 1984 from the Ministry of Agriculture, Fisheries and Food, have taken action to terminate the use of carbadox within their borders. Lastly, although FSIS has not reported finding a residue of carbadox in pork in several years, a recent article in Food Chemical News revealed that Canadian officials report a 5 percent violation rate for residues of the drug in that country. I have so far been unable to find an explanation for this apparent difference in violation rates in the two countries.

   It is clear from this admittedly incomplete summary that we cannot tell if consumers are being exposed to a greater than one-in-one million lifetime risk of cancer from the use of carbadox in swine.

   Recommendation

   The sponsor of carbadox should be given a rigid timetable for the submission of additional safety data that is sufficient to establish, and permit the monitoring of, conditions of safe use of their drug.

4. METHYLENE BLUE - In March, 1978, FDA withdrew the approval of drugs containing methylene blue for oral administration to cats and dogs because of both safety and efficacy problems. Shortly thereafter it became apparent that considerable amounts of the drug were being used off the label to treat cattle for nitrate poisoning. In order to make the drug available to veterinarians to treat this condition in cattle, Dr. Crawford, in 1979, wrote to at least one chemical company reassuring it that they could legally sell the dye to veterinarians. The Center also published a Drug Memo in March, 1979, advising veterinarians of their right to use methylene blue to treat nitrate poisoning in cattle even though the drug was not the subject of an approved NADA.

In October, 1984, upon learning that methylene blue was reported to give a positive response in several mutagenicity assays, I wrote a memorandum through HFV-100 to HFV-1 discussing the human food safety risks associated with the use of methylene blue in food-producing animals. I recommended in that memorandum that our scientists attempt to establish conditions of safe use of the dye and, at the same time, that they initiate a research project designed to find a more safe alternative drug to treat nitrate poisoning in cattle.

Recommendation

My memorandum of October 22, 1984 should be evaluated, revised if necessary, and implemented.

5. CHLORAMPHENICOL - Although the Center is proceeding with regulatory action against the sponsors of the oral solution formulation of chloramphenicol, I am concerned that, if this effort is successful, other dosage forms of the drug will replace the oral solution in the treatment of food-producing animals. A summary of the evidence that misuse is already occuring with chloramphenicol tablets and the basis for my concerns that such misuse will increase, were presented in a memorandum from me to HFV-200 dated June 14, 1984.

Recommendation

In view of the mounting evidence of their misuse, I recommend the Center issue assignments to the field and follow up with regulatory action against those who administer chloramphenicol tablets and capsules to food-producing animals. I also recommend the Center give serious consideration to withdrawing approval of all but the smallest of these tablets.

6. GENTIAN VIOLET - On December 7, 1982, following receipt of preliminary data on the carcinogenicity testing of gentian violet in mice at NCTR, representatives of CVM and the General Counsel's Office held a meeting to discuss options for action by the Center for terminating the exposure of consumers to residues of the dye in poultry. The memorandum of that meeting records a recommendation to Dr. Crawford that a FEDERAL REGISTER Notice be published declaring gentian violet to be not GRAS but a food additive or new animal drug depending on its intended use. At several subsequent meetings the wisdom of this approach was reaffirmed and, as far as I know, this is the option we are working towards today. At these meetings, Mr. Degnan, OCP-1, has never failed to point out that the Agency has a very small burden to successfully defend the position that a sponsored compound is not generally recognized as safe and that this burden appears to be clearly met by the results of the lifetime feeding study with gentian violet in mice.

Recommendation

I recommend that a scientist in HFV-100 who is familiar with the results of the carcinogenicity testing with gentian violet and another who is familiar with the results of the three total residue depletion studies conducted with the dye be given a joint assignment to work with Mr. Degnan on drafting a FR Notice on gentian violet. A reasonable time frame for circulation of an initial draft would be two weeks from the date of the assignment.

7. FENTHION - There are several approved NADAs for the use of this pesticide in and on cattle. After these approvals were granted, NTP conducted carcinogenicity studies with the drug that led the Bureau of Foods' CAC to conclude (memorandum of August 14, 1979) the compound was a carcinogen in mice. EPA was informed of our conclusion in 1981 and asked to comment on the feasability of joint regulatory action by our two Agencies against the pesticide and drug uses of fenthion. There is no record of any formal response from EPA in our files and the compound was apparently never placed on a list of problem drugs by FDA regulators.

Fenthion, as well as dibutyltin dilaurate and ronnel are examples of marketed drugs about which human food safety issues arose and then were forgotten with very little being done to address the issues. In some cases, the amount of drug reportedly sold each year was found to be rather low. With other drugs some additional evidence was found that at least partially addressed the original concerns. In these examples, however, definitive answers to the human food safety issues were not obtained and there are no memoranda in the record that lay to rest, in any definitive way, our food safety concerns.

Recommendations

I believe we need to somehow exhume and reexamine all marketed drugs that have been the subject of adverse findings since their approval. Some drugs - I suspect fenthion, dibutyltin dilaurate and ronnel might be in this category - will be found to not require immediate attention. Others may be found to present a significant human health hazard that should be taken care of as quickly as possible. Only when this has been accomplished can we prioritize in a meaningful manner, the work to be done on addressing food safety issues with market animal drugs.

Section II - RECOMMENDATIONS

This Section contains several general proposals for addressing the problems identified with specific drugs in Section I above.

I. I PROPOSE THAT WE REQUIRE SPONSORS OF MARKETED DRUGS TO ADDRESS SIGNIFICANT FOOD SAFETY ISSUES.

I understand that it was CVM's policy until several years ago to send letters to sponsors citing section 512(l) of the Act and requiring them to develop and submit to the Agency data addressing questions that arose concerning the safety and efficacy of their marketed drugs. This practice was discontinued, however, at least for food safety issues when the General Counsel's Office advised the Center that we might be successfully challenged in court if a sponsor decided to litigate our authority to require the development of data under Section 512(l) of the FFD & C Act. At the present time, we normally inform sponsors of marketed drugs of needed data only when we have made a commitment to publish an NOOH to withdraw approval of their NADA if the data requested are not forthcoming.

Because of resource constraints, and because hearings are so resource intensive, very few regulatory actions against marketed drugs are taken at any one time and, as noted above, the list of "problem drugs" about which the Center is doing very little or nothing, continues to grow longer each year.

Given the above, I believe we should consider reinstituting the procedure of formally asking sponsors of marketed drugs to provide the Center with data responding to human food safety issues that have arisen since the approval of their NADA. The data requested would be that needed to reestablish conditions of safe use of the drug using current standards of data collection. Sponsors that cooperated with us in providing the requested data would be assured of not having their marketed product subjected to a hearing to withdraw approval. Sponsors that did not agree to provide the requested data, or that did not meet agreed upon time frames for providing data, could be moved up in priority for regulatory action. The Agency's position in any regulatory action might well be strengthened by our having first given the sponsor an opportunity to address our concerns.

II. I PROPOSE THAT WE ADD ADDITIONAL EXEMPTIONS TO THE CENTER'S EXTRA-LABEL DRUG USE POLICY.

Certain aspects of the Center's Extra-Label Drug Use Policy are, in my opinion, insufficiently protective of human health. By adding to the list of exemptions to the Policy we can address these concerns without making any structual changes in the Policy itself. At present, the Center has made clear that DES, chloramphenicol and growth promotants may not be used in an extra-label manner. I propose that we add the following to our list of exemptions:

1. Any demonstrated or suspect carcinogen. The Center could list the specific marketed drugs, such as carbadox and nitroimidazoles, etc. that would simply present too great a human health hazard if their use were permitted in species or production classes of animals in which their conditions of safe use are not established.

2. Any extra-label use of a drug in lactating dairy cows for which the Center has not established a safe withholding period for milk and for which we do not have a regulatory method of analysis for residues in milk that can be used to

monitor the established withholding period. Certain sub-groups of the population consume more than twice as much milk as meat each day. Milk may constitute the whole diet of infants for a short period of time. Many drugs will partition in a way that results in much higher levels of residues in milk than will be found in the edible tissues of treated animals. For all of these reasons, it seems prudent that the Center not condone the use in lactating dairy cows, of drugs that do not meet the two criteria listed here.

3. We should also consider excepting from our Extra Label Drug Use Policy drugs that we know are handled differently in a non-approved than in an approved species. An example would be gentamicin, which requires 13 times longer to deplete to its tolerance in the bovine than it does in swine.

III. I PROPOSE THAT WE COMMIT ADDITIONAL RESOURCES TO THE PROBLEM OF MARKETED DRUGS THAT ARE NO LONGER SHOWN TO BE SAFE.

1. I urge that the Center ask the Commissioner for additional resources to carry out the prioritization of actions and evaluation of data that would be involved in accomplishing the activities recommended in this memorandum. I would be happy to contribute to a written or oral presentation making this request.

2. A second resource problem in PMS-70 is clear from the chart below of the number of professionals FTE's at three different dates; while the function was at the Bureau of Foods, shortly after transfer to CVM, and today. In my opinion the decrease in FTEs working in a CSO capacity represents a true efficiency introduced by this Center after the function was transferred. The 50 percent reduction in toxicologists working on HFS, on the other hand, has proven to be a real hardship. One reason for this is that several of our remaining toxicologists are in ill health. Another is that the Center has lost most of its expertise in several areas of toxicology, notably genetic toxicology and oncology. (It has been 11 months since Dr. Valcovic left FDA and we lost the valuable expertise that he brought to our petition review process.)

Differences of opinion often arise between drug sponsors and petition reviewers concerning the interpretation of scientific data. When this happens, sponsors hire the best available experts on the subject to argue their side of the issue. When the Center lacks the necessary expertise to effectively counter these arguments we are in danger of not being able to insure that safe conditions of use of a candidate drug will be established.

I urge the Center to give the highest priority to hiring several well qualified toxicologists; to insist that scientists now in our Division of Toxicology upgrade and expand their skills; and to identifying and engaging as consultants, outside experts who are familiar with food safety testing and evaluation.

REVIEWER AND SUPERVISORS WORKING ON HFS OF ANIMAL DRUGS

DATE	CSO	CHEMISTRY	TOXICOLOGY
1981	7	9.5^b	14
1982	6	10.0	10
1985	2.5^a	9.5^b	7

a) One half of HFV-102 plus 1 FTE in HFV-242 working on HFS issues for hearings.

b) The 0.5 represents Dr. Livingston's time devoted to HFS.

Joseph A. Settepani, Ph.D.

cc: HFV-1
HFV-100
HFV-101
HFV-102 (3)
HFV-140
HFV-150
HFV-201

Mr. Weiss. In October 1984, a recommendation was made that CVM publish a notice of opportunity for hearing to withdraw the drug from the market.

[The October 1984 memorandum containing this recommendation follows:]

Re-evaluation of the Status of Certain Marketed Drugs

There are several drugs currently being marketed for use in food-producing animals which have unresolved questions regarding the safety of their residues to the consumer. Some of these drugs are the subjects of current regulatory action by the Center and are listed below in the section entitled Ongoing Actions. The other drugs, listed below under the section Needed Actions, should be considered as potential areas of future action by the Center. They are described in the order in which the Office of New Drug Evaluation recommends them for the Center's priorities.

A. Ongoing Actions

1. Nitrofurans

Furazolidone, nitrofurazone, and furaltadone are members of a class of compounds called nitrofurans which are used at low levels in animal feeds as antibacterial and antiprotozoan agents. Nitrofurans also have prescribed therapeutic uses. The nitrofurans were first approved in the 1940's and they continue to be used extensively in food-producing animals, especially poultry and swine.

Questions regarding the safty of nitrofurans first arose in 1965 when scientists at the University of Wisconsin found that a substantial number of mammary tumors had developed in rats fed nitrofurazone. The scientists informed Norwich Pharmacal Company, at the time the sole American manufacturer of nitrofurans for food-producing animals.

As a result of these findings, Norwich ran two studies on the effects of feeding nitrofurans including furazolidone, furaltadone, nitrofurazone, and nihydrazone to rats for 45 weeks. These studies showed that rats fed nitrofurans had a significantly higher incidence of mammary tumors compared to controls. These data were submitted to the agency in June, 1967.

On March 31, 1971 (36 FR 5926 and 5927) the FDA issued notices of opportunity for hearing proposing to withdraw nitrofurazone and nihydrazone under the General Food Safety Clause based on the fact that these drugs were tumorigenic. Additional notices were published for furazolidone and furaltadone (36 FR 14343). All sponsors requested hearings.

The agency did not, however, hold a hearing. After reviewing additional evidence submitted after the publication of the 1971 notice, including four long-term feeding studies in rodents using furazolidone, the agency concluded that furazolidone was carcinogenic in rodents. The Center withdrew the original NOOH and published a second NOOH for furalzolidone on May 13, 1976 (41 FR 19907) proposing to withdraw approval of the drug under the Delaney Clause. On August 17, 1976 (41 FR 34891, 34899, and 34908) the Bureau published NOOHs for nitrofurazone, nihydrazone, and furaltadone proposing to withdraw their approvals under the General Food Safety Clause. All sponsors, except those for nihydrazone requested hearings. In an advance notice of hearing published on April 8, 1977 (42 FR 18660), the Commissioner announced that a formal evidentary hearing would be held on the proposals to withdraw approvals for nitrofurazone, furazolidone, and furaltadone.

The GAO investigated the FDA's handling of the nitrofuran situation in 1975-76. In their final report, GAO concluded that continued use of nitrofurans without data showing the absence of residues and of any cancer-causing nitrofuran metabolites in food may pose an imminent hazard to the health of man. However, the agency decided not to invoke the imminent hazard rule in the nitrofurans case but to proceed to a hearing as previously planned.

On September 4, 1984, the Commissioner published a Notice of Hearing for furazolidone proposing to withdraw the NADAs under both the General Food Safety Clause and the Delaney Clause. On the same day, the Commissioner published Notices of Hearing for nitrofurazone and furaltadone proposing to withdraw both of these drugs under the General Food Safety Clause.

The pre-hearing conference is scheduled to be held on November 19, 1984. The sponsors must file their narrative statements by November 5, 1984. The schedule for the hearing will be finalized at the prehearing conference; however, it is estimated that written direct testimony will probably be due February-March 1985 and cross-examination will probably take place during the Fall of 1985.

2. Estrogen

Synovex-S, first approved in 1956, and Synovex-H, approved in 1958, are implants containing estradiol benzoate and either progesterone or testosterone propionate, respectively. They are used in cattle for growth promotion and feed efficiency Esmopol contains estradiol monopalmitate which is injected into roasting chickens to produce more uniform fat distribution. It was approved in 1964.

Nearly all estrogens tested have been found to be carcinogenic in some species of animals Estrone, the principal metabolite of estadiol, has been widely used in experimental studies on carcinogensis. Testosterone by injection has caused cancer in some experimental animals and there is also some experimental evidence that progesterone is a co-carcinogen.

Based on these data, and the lack, despite a long-standing request to sponsors, of adequate information on residues incurred by these products, the agency issued notices of opportunity of hearing on January 5, 1976 (44 FR 1463) to withdraw the NADAs for Synovex-S, Synovex-H, and Esmopal. In addition, on the same day the agency issued a notice of opportunity of hearing on its proposed refusal to approve a new animal drug application for Steer-oid, which is an implant identical to Synovex-S.

All three firm's requested a hearing but only Syntex §Synovex S + H) and Mattox and Moore (Esmopal) submitted supporting information. In its request, Ivy-Gene (Steer-oid) incorporated by reference the data submitted by Syntex. Later they submitted their own residue data in support of approval of their NADA.

Syntex submitted data on residue levels of hormones in all four edible tissues of cattle following use of Synovex-S or H. They then argued that the low levels of estradiol, progesterone and testosterone to which one would be exposed to in meat as a result of the use of the Synovex products were insignificant compared to levels that are produced naturally by men, women, and children.

On the basis of the agency's evaluation this data, the Center together with CFSAN recommended that the Commissioner conclude that the Synovex products were safe even under conditions of possible misuse and that therefore a waiver be given for the requirement for a regulatory method. The rationale behind this recommendation is explained in detail in the Center's hormone policy.

In response to the 1979 NOOH, Mattox & Moore submitted a literature search regarding analytical methodology for estradiol. Residue data submitted to the agency for Esmopal-treated chickens were collected with the mouse uterine assay, a method whose sensitivity is not adequate for determining background levels of estradiol in chicken tissues. Therefore the Center has no data or information for Esmopal that it can use either to establish or confirm that the levels of estradiol remaining in the tissue will be similar to the levels left by the Syntex products. In fact, with regard to Esmopal, the levels in tissue may be significantly higher because the administered dose, on a dose per weight basis, is orders of magnitute greater than that given to cattle.

The Office of New Drug Evaluation has prepared a draft order to vacate the NOOHs for Synovex-S, Synovex-H and Steer-oid. They have also prepared an amended NOOH for Esmopal which provides that the collection of residue depletion data on Esmopal is necessary for any showing of safety of the product.

3. Chloramphenicol

Chloramphenicol was first approved in 1973 as an antibiotic for use in dogs and cats. Since it was not approved for use in food-producing animals, no residue data on chloramphenicol is available.

Shortly after the introduction of chloramphenicol in human medicine, reports appeared in the medical literature describing the relationship between use of chloramphenicol and the development of aplastic anemia. More than 700 cases of chloramphenicol-induced aplastic anemia have been reported in the United States since 1950. The occurence of aplastic anemia does not appear to be related to the frequency or level of exposure to the drug; rather it appears that 1 in 20-50,000 people are suspectible to this effect of the drug. Since chloramphenicol-induced aplastic anemia has not been demonstrated to occur in any animal other than man, a safe level for use of chloramphenicol cannot be established.

There is evidence demonstrating that extremely large amounts of chloramphenicol are being used in food-producing animals. For example, the USDA has found residues of chloramphenicol in calves. Because of this, the Center began an intensive educational program in 1983 to warn the veterinarians and food producers about the hazards to both the consumer and the drug handler of extra-label use of chloramphenicol in food-producing animals.

In addition, the Center has prepared an NOOH (which is in final draft) for the withdrawal of the NADAs for the oral solution of chloramphenicol in dogs on the grounds of misuse of this product in food-producing animals.

The Center still needs to make a decision on continued approval of other dosage forms of chloramphenicol for dogs, especially the large boluses. These is evidence of misuse of these forms in calves and their misuse will surely increase if the availability of the oral liquid is lost. Misuse of these forms of chloramphenicol will be harder to detect because there will be no injection site.

B. Needed Actions

1. Gentian Violet

Gentian violet has been marketed for use in animal feeds since 1951. Presently it is used in the feed of poultry to inhibit propagation of mold and fungus, although it has never been approved by the FDA for this use. The main component of gentian violet is crystal violet. Crystal violet belongs to a class of related dyes referred to as di-and triaminophenylamines. A few of these related compounds are known animal carcinogens and two, auramine and magenta, have been implicated as human carcinogens as a result of human exposures in the dye industry.

Gentian violet is mutagenic in assay systems using Bacillus subtiles, E. coli. and Salmonella tymphimurium. Crystal violet is also a demonstrated clastogen. Gentian violet belongs to a class of compounds which are demonstrated mutagens and, therefore, suspect carcinogens. In July, 1977, a meeting was held between representatives of one manufacturer of gentian violet, Marshall Minerals, Inc., and the Food and Drug Administration. The purpose of this meeting was for FDA to convey to Marshall Minerals the requirements for preparation of a satisfactory Food Additive Petition. On August 18, 1977, Marshall Minerals submitted a petition proposing that the food additive regulations be amended to provide for the use of a 1.60% gentian violet premix in poultry feed for the purpose of controlling fungus and mold growth. On January 23, 1978, the Center notified the sponsor that their petition was incomplete because all required information was not present (e.g. stability data), and consequently the petition would not be filed. The Center also informed the sponsor that they were reviewing the submitted data to determine its adequacy.

On May 8, 1978, the Center notified Marshall Minerals that they had reviewed the data that were submitted in the petition and that there were several inadequacies. The Center informed them that they were going to deny the petition unless, within thirty days, the sponsor remedy the inadequacies.

On July 7, 1978, Marshall Minerals submitted data purposting to resolve the inadequacies specified in our May 8, 1978 letter. These data did not resolve the serious shortcomings of the petition. Therefore, in a letter dated September 19, 1978 to Marshall Minerals, the Center explained in detail why the newly submitted evidence did not support approval of the FAP for gentian violet.

The agency denied the Marshall Minerals FAP for gentian violet on

March 30, 1979 (44 FR 19035) on the grounds that it lacked sufficient data to establish either safety to the Consumer or efficacy as a mold inhibitor. Marshall Minerals requested a hearing on this issue but did not supplement the record with data supporting their objections by the required date. Therefore, on March 28, 1980 $45 FR 20559), the agency denied them a hearing on the matter. Marshall Minerals appealed this decision and on November 16, 1981 the United States 11th Circuit Court of Appeals ruled that the agency had erred in denying the sponsor a hearing, that the agency must use the Delaney Clause rather than the Safety Clause as the grounds for denial, and that it was a disputed question as to whether gentian violet was a carcinogen. The court also ruled that the agency may not deny an FAP to Marshall Minerals for gentian violet on the grounds that it has not been shown to be effective. (661 F. 2no at 410.)

The agency petitioned for a rehearing on the matter because they believed that the court had misinterpreted the meaning of the General Food Safety Clause of the Act, but this petition was denied on February 23, 1982. Although the agency does not believe that gentian violet is safe, the agency has decided not to take regulatory action against manufacturers of gentian violet premixes used for mold inhibition provided the marketed products do not exceed the claimed use level of 8 ppm (47 FR 32480). This was an interium decision until the agency received the final reports from studies being conducted on the safety of gentian violet by NCTR.

In order to answer some of the safety questions surrounding use of gentian violet, NCTR, in the late 1970's - early 1980's began chronic feeding studies on gentian violet in rats and mice and also 14C-gentian violet residue depletion studies in chickens. In 1982, the preliminary report on the 14C-residue depletion study demonstrated that, at 5-days withdrawal, the concentration of gentian violet in the edible tissue of poultry, 1 ppb for muscle and 40 ppb for liver, exceeded the concentrations calculated as safe based upon the results of 90-day feeding studies. These concentrations are 0.1 ppb in muscle and 0.3 ppb in liver.

The results of the long term feeding study on gentian violet in mice were recently submitted to the agency. A preliminary review of these data indicated a significant dose-related trend in the incidence of hepatic tumors in both males and females with metatisises to the lung occurring in 14 of the treated animals. In addition, an increase in ovarian, uterine, and bladder tumors occurred in treated females.

The Division of Toxicology expects to submit their final evaluation of this study to the Center's Cancer Assessment Committee in the near future.

Recommended Course of Action

If the Cancer Assessment Committee decides that the data demonstrate that gentian violet is a carcinogen, a concentration of no carcinogenic concern should be calculated and this level compared with the results from the 14C-residue studies. If the actual residue levels at the proposed withdrawal time exceed the calculated safe level, the agenqy should begin formal rulemaking procedures under 21 CFR 10.50 to declare gentian violet a food additive. This would require the sponsors of gentian violet to obtain an approved FAP in order for their product to be marketed.

2. Carbadox

Carbadox has been approved since 1972 for use in baby pigs for weight gain and improved feed efficiency and to control swine dysentary and bacterial swine enteritis. It has a 70 day withdrawal time.

Carbadox is rapidly metabolized to methyl carbazate with quinoxaline-2-aldehydye as an intermediate, and also to quinoxaline-2-acid with desoxycarbadox as a metabolite. In addition, metabolites of carbadox may be covalently bound.

Two year chronic bioassays in rats have demonstrated that carbadox and desoxycarbadox are hepatocarcinogens. Extrapolation of these data give a concentration of no carcinogenic concern for carbodox of 318 ppt in muscle an 954 ppt in liver and for desoxycarbadox of 183 ppt in muscle and 549 ppt in liver. In addition, carbadox has been shown to be mutagenic in a number of different assay systems including Ames tester strains TA 98 and TA 100 without activation. Carbadox causes gene mutations in E. coli and pneumoniae, and is positive in the unscheduled DNA repair test and the mouse micronucleus test. Carbadox also causes chromosomal aberrations in the in vitro mouse cytogenetics assay. Desoxycarbadox is mutagenic in Ames tester strains TA 1535 and TA 100 with liver S-9 activation.

Neither methyl carbazate nor quinoxaline-2-aldehyde are mutagenic when tested singly in the Ames test but do cause mutation induction in TA 1535 when mixed together in the presence of Arochlor-induced rat liver S-9 fraction. In addition methyl carbazate may be converted to a hydrazine. In the literature, hydrazines have been shown to cause hepatic cell carcinomas in rats and pulmonary adenomas and adenocarcinomas, and heptomas and carcinomas in mice.

Quinoxaline-2-carboxylic acid comprises-approximately 25% of the residue of carbadox on limited study which the sponsor submitted. However, these residue studies extend to only 21 days post treatment. Quinoxaline-2-carboxylic acid has been tested in chronic bioassays using both rats and mice. Data from both studies demonstrated that quinoxaline-2-acid was not an oncogen. The determinitive and confirmatory assays for carbadox use quinoxaline-2-acid as the marker substance and are acceptable at the 30 ppb level.

Recommended Course of Action

Although carbadox and one of its metabolites are carcinogenic, limited residue studies submitted by the sponsor indicated, in the opinion of the Chemistry division, that these residues may not be present above the level of concern at the withdrawal time of 70 days.

The agency should form an intial carbadox task force and meet with the sponsor to discuss the agency's safety concerns regarding carbadox. The agency should request total residue depletion data and metabolite identification up to 70 days withdrawal to determine if the percent of residue not present as quinoxaline-2-acid is below the estimated concentration of no carcinogenic concern at the time of slaughter. A definite timetable for submission of the data should be established with the sponsor with the clear understanding that the agency will proceed to a hearing if the data are not forthcoming.

3. Nitroimidazoles

A. Dimetridazole

Dimetridazole was first approved in 1964 in turkeys for the prevention of blackhead and for growth promotion and feed efficiency. A five day withdrawal period is required. The sponsor has requested an approval for use of dimetridazole in swine.

Concerns about the safety of dimetridazole first arose when the agency learned of the results of a study at University of Wisconsin which demonstrated that female rats fed dimetridazole had an increase in mammary fibroadenomas. As a result of this study, the agency requested that the sponsor submitted an analytical method capable of measuring residues of dimetridazole to 2 ppb. The sponsor submitted a GLC method using the hydroxyl metabolite of dimetridazole as the marker residue. No total residue information was submitted nor could the method pass validation trials. USDA was unsuccessful in developing its own method for measuring residues of dimetridazole.

In 1976, the sponsor submitted the results of a chronic (122 wk) feeding study in rats which demonstrated that dimetridazole caused significant increases in benign mammary tumors in the mid-and high dose females and in the high dose males. Extrapolation of this data gave a virtually safe dose in the low ppbs.

The agency terminated the investigational authorizations for dimetridazole in 1976 and requested that the sponsor submit a second chronic bioassay in rodents.

In addition to the data which demonstrated that dimetridazole is tumorigenic, it has also been shown to be mutagenic in several assays systems including Salmonella typhimurium tester strain Ta-153, LT-2 is G46, Klebsiella pneumoniae, Escherichia coli and Citiobactor freundu. In addition, nitromidazoles as a class are suspect carcinogens and are also structurally related to other class of suspect carcinogens, the nitrofurans. Based upon their knowledge of nitroimidazole, the Division of Chemistry has concluded that total residues of dimetridazole at the proposed withdrawal time are equal to or greater than 1 ppm. In addition, from data on other nitromidazol such as ronidazole, they concluded that parent drug and/or the hydroxyl metabolite are not adequate for monitoring total residues of dimetridazole because their half-lives are very short in comparison to that for the total residue.

B. Ipronidazole

Ipronidazole was approved in 1971 for use in turkeys for the prevention of blackhead and for increased weight gain and improved feed efficiency. The sponsor has requested approval of ipronidazole in swine.

In 1978, the sponsor submitted a two year chronic feeding in rats to the FDA which demonstrated a statistically significant positive trend in mammary tumor development in treated female animals.

The sponsor submitted the results from a second chronic feeding study in mice in 1982. Because of a compound-related increased incidence of hyperplastic and neoplastic lung lesions in both male and female animals, this study has been referred to the Cancer Assessment Committee for final evaluation. Additional data were requested of the sponsor in 1983 which were submitted to the agency in 1984.

The sponsor also submitted the results of five mutagenicity assays using ipronidazole. Two of these, the Ames test and the host-medicated cell assay, demonstrated that ipronidazole was mutagenic. The results from the remaining three studies were inconclusive.

The sponsor has validated to the 2 ppb level a GLC method of analysis for the 2-hydroylated metabolite of ipronidazole. Their studies demonstrated that this metabolite depletes to below 2 ppb after 3-4 days withdrawal. However data from other nitroimidazoles such as ronidazole indicate that parent drug plus the hydroxylated metabolite are a small fraction of the total residue of ipronidazole in the target tissue, liver, and that therefore it is unsuitable for monitoring total residues of ipronidazole. No confirmatory assay has been submitted.

C. Recommended Course of Action for Nitroimidazoles

If the Cancer Assessment Committee decides that ipronidazole is a carcinogen, then a notice of opportunity of hearing should be prepared for withdrawal of ipronidazole under the Delaney Clause. A second notice of hearing should be published at the same time for dimetridazole proposing to withdraw this drug under the General Food Safety Clause. If the CAC decides that ipronidazole is a tumorigen, then withdrawal of both drugs should be proposed under the General Food Safety Clause.

A single hearing should be held on the nitroimidazoles such as the agency is doing for the nitrofurans. No actions should be taken on nitroimidazoles until the nitrofuran hearing is complete because withdrawal of these products would support the agency's position that nitroimidazoles are unsafe. In addition, most of the expert witnesses for nitrofurans could also testify in nitroimidazole hearings. Also the Center has only resources for one major hearing at a time.

However, since there is evidence that misuse of both ipronidazole and dimetridazole in swine is widespread, some interium measures should be instigated to deal with this problem until a hearing can be held. The Center should investigate the possibility of establishing a more vigorous compliance program to deal with misuse of these compounds in swine.

4. Dibutyltin Dilaurate

Dibutyltin dilaurate has been used since the early 1950's in poultry for the prevention of coccidiosis and for improved feed efficiency. It has a 7-day withdrawal time.

Dibuityltin dilaurate-containing drugs were deemed by the NAS/NRC review to be probably effective with the requirement that the NADAs be supplemented with additional efficacy data. Therefore in 1959 FDA declared dibutyltin dilaurate to have "not a new drug" status.

Because the firms did not submit adequate data on effectiveness, the agency published an NOOH on August 29, 1978 proposing to withdraw the NADA for Polystat 3 (which contains dibutyltin dilaurate) because of a lack of both effectiveness data and data to support a safe withdrawal time. Intially the firm requested a hearing; however subsequently, in 1981, the firm asked that the NADA be withdrawn without a hearing. Notice of withdrawal of the NADA was published in 47 FR 5466. However DERs for April 1984 indicate that products

READEX FICHE

containing dibutyltin dilaurate are still being actively marketed under other NADAs.

In 1979, the Bureau of Foods' Cancer Assessment Committee analyzed the results of an NTP chronic bioassay in mice on a related compound, dibutyltin diacetate. They concluded that a significant dose-related increase occurred in the incidence of heptocellular ademomas in the combined data from male and female animals. Based upon these findings, the CAC concluded that dibutyltin dilaurate could be classified as a suspect carcinogen. Related compounds have also caused suppression of thymus-dependent cell-medicated immunity when fed to rats for six weeks.

The sponsors have not submitted adequate residue or toxicology data to determine safe conditions of use for dibutyltin dilaurate.

Recommended Course of Action

The agency should form a initial core dibutyltin dilaurate task force to meet with the sponsor to discuss the agency's concerns regarding the safety of this product. The agency should request additional data including two-year chronic bioassays in rodents and adequate residue data to establish a withdrawal time. A reasonable timetable, including interium reports, should be established with the sponsor for submission of the data with the understanding that the agency will proceed to withdraw their product should they not meet their data commitments.

5. Ronnel

Ronnel has been used since the 1950s in cattle for the control of grubs, lice, and horseflies. A potential contaminant of ronnel, 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD), has been demonstrated to be a carcinogen in a 2 year chronic bioassay in rats. Using the linear "one-hit" model of extrapolation, the Center has estimated a safe concentration for TCDD of 0.15 ppt in muscle and 0.03 ppt in liver. The sponsor has developed a method for measuring TCDD in tissues at 5-10 ppt.

The sponsor has demonstrated that no TCDD can be detected in ronnel at the level of 5-10 ppb. However the agency has made a worst case estimate that 10 ppb of TCDD in ronnel could result in residue levels in cattle of 0.37 ppb in liver and 0.02 ppb in muscle at zero withdrawal.

Recommend Course of Action

Since the agency has very little evidence, at the present, to support their concerns regarding the safety of ronnel, the initial action taken should probably be to send a regulatory letter to the sponsor requesting either information as to the level of TCDD in ronnel or that the sponsor reformulate their product to eliminate the TCDD.

If the sponsor submits the requested data, the Center could re-evaluate their safety concerns in light of the new information. If the sponsor is unwilling to submit the data, the Center should consult with General Council as to the regulatory options open including possible adulteration or misbranding charges against the product.

C. Overall Recommendations

The Center needs to establish a committee to make some recommendations as to where marketed drug re-evaluation should fit in the overall list of Center priorities. In addition the Center should revise the order of their list of needed actions on marketed drugs as new concerns arise about the safety of marketed drugs and also formalize a consistent strategy for dealing with these issues.

Mr. WEISS. Is this known carcinogen still on the market?

Dr. CRAWFORD. Yes, it is. We have responded to the recent information about it, including the October 1984 memorandum, by placing it on the list of compounds to be considered for action.

As you know, Mr. Chairman, our administrative process does require the implementation of an administrative hearing before an administrative law judge in order to take these kinds of actions. The documentation for that takes time and the considerations involved are complex. These become, basically, legal decisions in a courtroom setting.

Mr. WEISS. Right. But the first study submitted to FDA showing that that drug induced mammary tumors in rats goes back to 1978.

Dr. CRAWFORD. That is correct.

Mr. WEISS. So it seems to me that you would have had ample time to take note of the warning signs that were present in that study.

Another drug used in turkeys, dimetridazole, was conclusively shown to be a tumorigen several years ago. In an August 18, 1982, memorandum, Dr. Robert Gillespie of the Division of Toxicology recommended that the drug be removed from the market.

[The memorandum referred to follows:]

~~August 18, 1982~~ [illegible]

Division of Toxicology/BVM
HFV-330

Dimetridazole — Casual Review
~~[illegible]~~
~~[illegible]~~
Division of Food Animal Additives, HFV-320

The following petitions relate solely or in part to the above subject.

Food Additives Master File # 26
Food Additive Petition # 1092
Food Additive Petition # 1152
Food Additive Petition # 1153
Food Additive Petition # 1942

Salsbury's Laboratories
Charles City, Iowa
(AF# 12-387)

Investigational New Animal Drug Application 64
Investigational New Animal DRug Application 886
Investigational New Animal Drug Application 938

Investigational New Animal Drug Application 1838

Hess & Clark
Ashland, Ohio
(AF# 13-036)

Approves NADA's

NEW ANIMAL DRUG APPLICATION No. 14-613
NEW ANIMAL DRUG APPLICATION No. 14-145
NEW ANIMAL DRUG APPLICATION No. 14-345

Salsbury Laboratories
Charles City, Iowa
(AF# 12-387)

Unapproved NADA's

NEW ANIMAL DRUG APPLICATION No. 93-534
NEW ANIMAL DRUG APPLICATION No. 93-535
NEW ANIMAL DRUG APPLICATION No. 96-406
NEW ANIMAL DRUG APPLICATION No. 97-038

Hess & Clark
Ashland, Ohio
(AF# 13-036)

Thru: R. E. Osterberg, Ph.D.
T. M. Farber, Ph.D.

Introduction

Dimetridazole is a member of the 5-nitro imidazole family with the following formula.

Several related compounds are known. Among them are ipronidazole, metronidazole and ronidazole. Ronidazole is carcinogenic and has not been approved for use in food producing animals. Metronidazole (Flagyl) is a human drug not used in animals at least in the UNited States.

It is believed to be a carcinogen based on the work of Dr. Phillipe Shubik et al at the Epply Institute for Cancer Research. Data on ipronidazole are currently under review. It is definitely tumorigenic but a final evaluatio.as to whether it is a carcinogen has not been made as yet, however, it has been shown to be a mutagen.

Salsbury Laboratories NADA's for soluble poder, feed premix and tablets of Dimetridazole were approved in 1964 for control and treatment of blackhead in turkeys.

In 1971, the Division of Toxicology became aware of the data from Bryan et al., University of Wisconsin indicating that dimetridazole produced benign mammary tumors in female rats. We asked Salsbury Laboratories to develop an analytical method sensitive to 2 ppb. They proceeded to do this and developed a method that apparently worked in their laboratory but failed validation trials.

In 1974, Hess and Clark submitted petitions for use of dimetridazoie to treat swine dysentery and included a polarographic method of analysis sensitive to 2 ppb for what they considered to be the major and longest persisting metabolite. They showed depletion to 2 ppb in about 6 days. However, total reside studies indicated they were in the area of 1 to 1.5 ppm of radioactivity which remained in some of the tissues. This residue has not been identified, and as a result, their petition has not been approved.

The following is a summary of the available toxicology. Most of it has been submitted by Salsbury Laboratories and Hess & Clark but some and particularly the mutagenicity studies have been secured from a search of the literature of Medline, Toxline and Cancerline.

DIMETRIDAZOLE TOXICOLOGY STUDIES

I. General Pharmacology

Submission: NADA 93-535

Initial Evaluation: None done

Species/Strain: Dog

Pretreatment: Anesthetized with chloralose or pentobarbital.

Compound: Dimetridazole

Route: Oral (50 to 200 mg/kg as a 10% suspension in gum).

[illegible]

Results: Presented in a summary form.

1. Effect on arterial pressure

In the dog the compound causes a slow progressive lowering (up to 20% fall) in arterial pressure at dosages from 100 to 200 mg/kg orally and slight lowering at a dosage of 10 mg/kg intravenously.

2. Effect on electrocardiogram

In the dog dimetridazole (at 100 mg/kg p.o.) causes a detectable rise in rate of heart beat. The rate of beat rises from 170 to 270 beats per minute in the 3 hours following ingestion of the drug. At this time a rise in voltage of T and P occurs showing probably a strong increase in cardiac work. At 200 mg/kg the cardiac phenomena are also seen but appear to regress more quickly.

II. ACUTE TOXICITY

Test Substance	Species	Sex	Route	LD_{50} (mg/kg) Remarks
Tech.	Rat	-	Oral	1600 (1576-1856)
Tech.	Mouse	-	Oral	2000 (1660-2420)
Tech.	Mouse	-	Oral	1750
Tech.	Mouse	-	Oral	1790*
Tech.	Dog	-	Oral	500*
Tech.	Chicken	-	Oral	1250
Tech.	Turkey	-	Oral	500
Tech.	Turkey	-	Oral	325*
Tech.	Mouse		I.V.	290 (225-328)
Tech.	Rabbit	-	Dermal	No irritation occurred
1% aq. soln.	Rabbit	-	Ocular	No irritation occurred
Soluble Form.	Rat	-	Oral	2500 (2000-3125)**
Soluble Form.	Mouse	-	Oral	1700 (1462-2125)**
Soluble Form.	Rat	-	I.V.	70 (66-75)**
Soluble Form.	Mouse	-	I.V.	60 (54-67)**
Soluble Form.	Rabbit	-	Dermal	No irritation occurred
Premix	Rabbit	-	Dermal	No irritation occurred

*administered for 5 days
**expressed in terms of the technical

Soluble Fomulation-"Emtryl" soluble= 40% dimetridazole
22% potassium dihydrogen phosphate
38% potassium sulphate

Premix= "Emtryl" premix= 22.5% dimetridazole
67.5% calcium carbonate
10% calcium phosphate

III. SUBCHRONIC TOXICITY Salsbury Labs.

1. Assay: 3-Month Oral Toxicity Study

Submission: INAD 64

[illegible] Test substance [illegible]

Species/Strain: Rat Simonsen albino

No./Sex/Group: 10

Dose Levels: 0, 2000, 4000, 6000, 8000 and 10000 ppm
200, 400, 600, 800 1,000 mg/kg

Duration: 3-Months

Route of Admin. Oral (diet)

Results: No adverse effects were observed. [illegible]
(This was only a summary).

NEL: less than 2000 ppm based on histopath

Comments:

2. Assay: Repeated Administration to Dogs

Testing Lab. Salsbury Laboratories, Charles City Iowa

Submission: NADA 93-535

Initial Evaluation: Not evaluated

Test Substance: Dimetridazole

Species/Strain: Dog Beagle

No./Sex/Group: 2 animals/group (sex not reported)

Dose Levels: 50 and 100 mg/kg/day

Duration: 50 mg/kg/day (30 days); 100 mg/kg/day (sporadic administration over a 34 day period).

Route of Admin: Oral (gavage)

Results: Body weight was decreased in animals administered 100 mg/kg/day. One dog in the 50 mg/kg/day group and both dogs in the 100 mg/kg/day group exhibited marked ataxia dominated by hypertonic crises, i.e. stiffness of the tail, tonic extension of the posterior limbs then tonic extension of the anterior limbs, and stiffness of the neck. This was accompanied by convulsive or subconvulsive (tonic-clonic movements, trembling) and sometimes nystagmus. There was a decrease in urinary volume at 100 mg/kg/day. One dog in the 100 mg/kg/day group had slight glucosuria and the presence of bile salts and pigments in the urine. Small hemorrhages were observed in all animals in the gray substance (at the level of the anterior horns) of the spinal cord.

NEL: ≤50 mg/kg/day

LEL: 50 mg/kg/day (neurological effects)

Comments: The study is not acceptable. A NEL was not demonstrated.

3. Assay: Repeated Administration to Rats

Submission: NADA 93-535

Initial Evaluation: Not evaluated

Test Substance: Dimetridazole

Species/Strain: Rat Simonson Albino

No./Sex/Group: 10 animals/group (sex not reported)

Dose Levels: 50 and 100 mg/kg/day

Duration: 30 days

Route of Admin: Oral (gavage)

Results: No adverse effects were observed

NEL: 100 mg/kg/day

Comments: The study is not acceptable. The duration of the study was only 30 days.

The following summaries were provided in NADA 93-535.

In trials investigating the growth-promoting activity of dimetridazole, the drug was found to produce no apparent toxic effects when administered to growing pigs at concentrations from 0.005 to 0.0625%. Italian studies in which dimetridazole at amounts of 0.0015, 0.003, 0.006 and 0.012% was fed to pigs for two months, revealed no apparent toxic effects.

Dimetridazole administered orally to cows during trials in the control of bloat in New Zealand resulted in a temporary reduction in appetite. When lactating cows at pasture were dosed with 60 g dimetridazole daily for three days, treatment being repeated at weekly intervals for three weeks, a moderate but temporary fall in milk yield occurred after the third course of treatment. It is acknowledged that dimetridazole suppresses rumenal fermentation.

at dosages up to
five days. No
severe symptoms
observed
at [illegible] shown [illegible]

A solubilized form of dimetridazole was

indigestion in some animals.

Dogs will tolerate a level of 12.5 mg/kg continuously for 3 months without ill effect.

Daily dosages of 100 mg/kg given continously for three months in the diet had no suppressive effect on the growth rates nor any adverse effect on the function of liver or kidney or of the central nervous system of rats. No abnormalities were revealed in histological examination of other tissues.

Experiments in which dimetridazole was fed at levels of 0.025% and 0.05% to growing turkeys for 24 weeks have shown that such levels of the drug significantly improved growth. At 0.10% dimetridazole retarded growth in the first eight weeks but slightly improved weight gains over the 24-week period. At 0.2% dimetridazole retarded growth and after 5 weeks toxic symptoms appeared. 87% mortality was observed in this group.

High levels of (0.1 to 0.4%) of dimetridazole were fed continuously in the diet for 4 to 6 weeks to day-old chicks. Toxic symptoms appeared after about 10 days in the group receiving 0.3% and 0.4% of the drug, but the only effect of administering 0.1% and 0.2% was some depression in weight. Normal growth ensued when the birds were placed on ordinary diets.

Local tolerance studies in rabbits showed that dimetridazole caused no local irritation to the skin.

4.	Submission:	NADA 93-535
	Testing Lab.	Salsbury Labs.
	Species/Strain:	Rat Simonsen Albino
	No./Sex/Dose:	5
	Age:	Weanling
	Compound:	1, 2, dimethyl-5-nitroimidazole (dimetridazole)
	Dose level:	0, 50, and 100 mg/kg
	Duration:	90 days
	Route of Admin.:	Oral in diet

Observations

A. In Life

Growth rate:	Intervals not stated
General health:	Intervals not stated
Urinalysis:	pH, blood, bilirubin, glucose, sediment, intervals not stated.
Clinical chemistry:	Not done
Hematology:	Not done

B. Post Mortum

Gross Pathology:	Not done
Organ weight:	Not done
Histology:	Brain, spinal cord (cervical dorsal, lumbar) pituitary, thyroid, thymus, salivary gland, lung heart, liver, spleen, pancreas, adrenal, kidney, stomach, intestine, bone marrow, skeletal muscle, testicle, seminal vesicle, ovary, uterus.
Results:	No adverse effects observed on growth or general appearance. No histological abnormalities seen.
No-effect level:	100 mg/kg
Comment:	This study is inadequate to assess the subchronic toxicity of dimetridazole. Too few animals were used, and after the interim sacrifice only 3 survivals/sex/dose level were retained. Too few parameters were assessed.

5.	Submission:	NADA 93-535
	Testing Lab.	Salsbury Labs.
	Species/Strain:	Dog/Beagle
	No./Sex/Dose:	1
	Route of Admin.:	Oral (stomach tube 5 days/week in diet 2 days week.

Age at start of study:	Not reported
Dose levels:	12.5 and 50 mg/kg
Duration of study:	90 days

Observation

	[illegible], general health. [illegible] not reported.
	Hematology pretest, consisting of RBC, WBC total and differential, reticulocyte count, Hgb, Hct, ESR.
	Clinical chemistry pre-test consisting of BUN, glucose, alkaline phosphatase, bilirubin, plasma protein, SGOT, SGPT.
	Urinalysis pretest for pH blood, bilirubin, glucose, sediment.
	All animals served as their own controls.
B. Post Mortum:	Histology of brain, spinal cord (cervical, dorsal, lumbar) peripheral nerves, salivary glands, thyroid, pituitary, heart, lung, liver, spleen, pancreas, adrenal, kidney, stomach, intestine, skeletal muscle, testicle, uterus, ovary
	Gross pathology- not done Organ weights- not determined

Results:

Appearance:	Widely distended irises and excitement in all dogs after seven weeks of drug treatment. Contraction of extensor hind leg muscle with inability to walk normally in high-dose male at eleven weeks.

Clinical Chemistry:	No adverse effect reported
Hematology:	No abnormalities reported
Urinalysis:	No abnormalities reported
Histology:	All organs examined in the low dose animals were histologically normal. At high dose there was evidence of chronic pyelonephritis and fatty changes in the liver. One animal showed a hypocellular bone marrow. One animal had an abnormally staining thyroid. No other abnormalities were reported.
No effect level:	12.5 mg/kg
Comment:	This study is inadequate to determine the subchronic toxicity of dimetridazole. No control animals were used, and only one animal per dose were used in the study. The sponsor did hematology, clinical chemistry and urinalysis pre-test, but it is not apparent whether these tests were performed [illegible]

addition, too few parameters were examined.

6. Project No. 125, Trial DST 3A-62

Initial Submission: NADA 93-535, Vol. 4 p. 082

Testing Lab. Salsbury Lab.

Initial Evaluation: March 19, 1982

Test Substance: Dimetridazole

Species/Strain: Dog, Beagle

No./Group: 1/sex/group

Age at Start: 3-8 months

Dose Level: 3600 and 10,800 ppm (corresponding to 90 and 252 mg/kg)

Duration: 30 days

Route of Admin.: Oral (diet)

Results: After 2 weeks, ataxia was observed in both dogs at 10,800 ppm. No deaths occurred. At termination, feed intake had been reduced at upper dose and both dogs exhibited kidney changes (nephrotic cortex, capsule adhering somewhat to cortical tissues, petechial hemorrhages in cortex and liver changes including mild congestion and small hemorrhages with either central lobular degeneration or early cirrhosis: organ weights of major organs were taken but the data were not presented.

NEL: 3,600 ppm

Comments: The firm only intended this study as a range finding study in anticipation of a comprehensive subacute trial.

7. Project 125, Trial No. RST-25-62

Initial Submission: INAD 63, Vol. 1, p 273

Initial Evaluation: Reviewed in Summary by L. S. Andrews, Ph.D.

Report No./Date: None/9/8/80

Laboratory: Dr. Salsbury's Laboratories

Test Substance: Dimetridazole

Species/Strain: Rat/not stated

[illegible]

5/sex/Group 10/sex/group

0 200 400 600 800 & 1,000 mg/kg

Dose Levels: 0, 2000, 4000, 6000, 8000 and 10,000 ppm in diet.

Duration: 90 days

Route of Admin.: Oral (diet)

Results: Three females at 10,000 ppm died on test. Observations at necropsy on gross tissues and on histological slides disclosed a dose-related atrophy and degeneration of testes. All doses also produced decreases in body weight gain. In males, feed efficiency was markedly impaired at the 3 highest doses while in females, feed efficiency was impaired at all doses. Statistical analyses were not provided.

NEL: Not demonstrated

Comments: Toxicity was observed at all doses in either or both sexes. NEL was not seen.

Project 128, Trial No. DST-3-62

Initial Submission: INAD 64, Vol. 1, p. 19

Initial Evaluation: Reviewed in Summary by L. S. Andrews, Ph.D.

Report No./Date: None/ 9/14/60

Laboratory: Dr. Salsbury's Laboratories; Iowa.

Test Substance: Dimetridazole

Species/Strain: Dog/Beagle

Age of Animals: Not stated

No./Sex/Group: 2 dogs/sex/group

Dose Levels: 0, 16, 33, 66 and 132 mg/kg/day

Duration: 90 days

Route of Admin.: Oral (Capsule)

Results: Emesis occurred at 33 mg/kg. Ataxia was observed at 66 and 132 mg/kg and at these 2 dose levels, histologic examination disclosed "mild" kidney and testicular changes at 66 mg/kg; 25% of the animals expired. At 132 mg/kg, 100% of the animals expired. Feed intake was reduced at 66 mg/kg. Statistics were not provided.

-14-

NEL: 16 mg/kg/day

Comments: A variety of other pathologic changes occurred in control and treated animals alike and were stated to be unrelated to treatment. I agree with the reviewer that the study is inadequate.

Results: Hyperexcitability and bloodshot eyes were observed in treated dogs after 7 weeks. During week 11, the male dog at 50 mg/kg became uncoordinated and exhibited rigidity of muscles in hind limb, tail and abdomen which persisted for 1 week. Gross and histopathologic examination did not disclose any abnormalities. Statistics were not provided.

-15-

NEL: Not demonstrated

Comments: The study is still considerd to be inadequate.

Project 128, Trial DST-3-62

Initial Submission: NADA 93-535, Vol. 4 p 094

Initial Evaluation: Reviewed in Summary by Mr. Stanton C. Lovre and additional attached review of R. L. Gillespie, DVM.

Report No./Date: None/ 9/20/80

Laboratory: Dr. Salsbury's Laboratories, Iowa

Test Substance: Dimetridazole

Species/Strain: Dog/Beagle

Age of Animals: 12-30 weeks

No./Sex/Group: 2/sex/group except that at the lowest dose, 4 males only were tested.

Dose Levels: 0, 16, 33, 66 and 132 mg/kg/day

Duration: 100 days

Route of Admin.: Oral (gelatin capsule)

-16-

Observation: Body weights were recorded twice weekly. Food consumption was monitored. Behavioral and motor effects were observed at unstated intervals. Hematology, performed at 30 and 60 days and at termination

hematocrit, hemoglobin
— . TOTAL AND Differenti
WBC cell cou
and

sedimentation rate. Chemistry consisted of blood urea nitrogen only. Gross pathology and histopathology were performed on animals killed in extremis and at termination. Samples of the following organs were prepared for histopathologic examination: adrenals, bone and bone marrow, brain (several regions), gall bladder, heart, intestine, kidneys, liver, lung, various lymph nodes, spinal cord, pituitary, spleen, stomach (cardiac, fundic and pyloric regions) testes, thymus, thyroid, urinary bladder, pancreas, oviducts and intestine (colon, duodenum, jejunum, cecum and ileum).

Results: Two dogs died on test (males treated at 66 and 132 mg/kg). Three dogs were killed in extremis. Ataxia and incoordination were observed in several dogs at these 2 doses. In the 66 mg/kg group, weight gain and feed intake were reduced.

Pathologic changes are recorded with the number of observations:

32 mg/kg/day: Brain necrosis (1), lesions in cecum (1), cortical nephrosis (4) and adherent capsule (1), depressed atelectatic area of left lobe of lung (1) and multiple atalectic areas (1), congested and hemorrhagic lungs (2), hemorrhagic spleen (1), and stomach hemorrhage in pyloric region (2).

6 mg/kg/day: cortical nephrosis and adherent capsule (1), stomach hemorrhage in pyloric region (1)

Additionally, in the group treated at 132 mg/kg/day, the kidneys exhibited moderate cloudy swelling in cells lining the convoluted tubules and tubules comprising the medullary ray. Hyaline material containing a small quantity of granular substance occurred in the tubule lumina to a mild degree being greatest in the order 132   66   33 mg/kg. Dose-related reproductive changes were observed in testes which increased in severity with dose, in all groups, including atrophy of the seminiferous tubules, absence of mature spermatocytes and moderate cellular degeneration of spermatids.

All laboratory analyses were within normal ranges.

[illegible] males [illegible]

[illegible]

Comment:	The study exceeded requirements of core standards except for failure to test females at the lowest dose. DT is currently in agreement with the reviewer concerning this aspect.

Project 125, Trial No. RST-25-62

Initial Submission:	NADA 93-535, Vol. 4, p. 153
Initial Evaluation:	Reviewed in Summary by Mr. Stanton Lovre
Report No. Date:	None/ 9/20/80
Laboratory:	Dr. Salsbury's Laboratory, Iowa
Test Substance:	Dimetridazole
Species/Strain:	Rat/Simonsen Albino (SPF)
Age of Animals:	6 weeks
No./Sex/Group:	10

Dose Levels:	0, 100, 200, 300, 400 and 500 mg/kg/day (corresponding to 0, 2000, 4000, 6000, 8000, and 10,000 ppm in diet). (Control feed was restricted evidently to intake of highest dose group).
Duration:	90 days
Route of Admin.:	Oral (dietary)

rvations as follows:

Toxic signs:	Frequency of observations is not stated for behavioral and motor effects.
Survival:	Deaths are shown cumulatively at termination.
Body Weight:	Weight gain, feed consumption and feed conversion were measured at unstated intervals.
Clinical Laboratory Analyses	Hematology was performed pretest and at weeks 4, 8 and 12 including analyses for packed cell volume, hemoglobin, red blood cell count and total and differential white cell count. Urinalyses were performed at an undisclosed frequency.
Necropsy:	At termination, remaining animals were examined. Tissues were also removed and examined from animals which died during the study. Organ/body weight ratios were recorded for at least one group. Samples of the following organs were taken from [illegible] at termination: adrenals. Brain

termination: adrenals, brain, heart, intestine, kidneys, liver, lymph nodes, pancreas, ovaries, skin, section of spinal cord, spleen, sections of stomach, testes, thyroid, urinary bladder, duodenum, jejunum and cecum.

istics: Data on body weight, feed consumption, feed conversion and organ/body weight ratio were analyzed by Standard Analyses of Variance and Duncan's Multiple Range test.

Results: Data on body weight, feed consumption and feed conversion were collected but were not provided with the report. Organ weight/body weight rations were presented for only 1 male and 1 female group of treated animals.

Mortality: Three females at 500 mg/kg/day died on test and the remaining 137 animals were killed for necropsy and histopathology.

Toxic Effects: Ataxia and violent spasms were observed for 4 weeks in those animals dying on test. Urine was positive for protein in undesignated animals at dose levels of 8000 and 1000 mg/kg/day at undesignated intervals.

Gross & Histopathology: For the 3 females which died on test, dark livers and hemorrhagic kidneys were observed. For animals killed at termination, changes observed included possible kidney involvement, slight ovarian toxicity and drug-related decreases in testicular weight. The lowest effect dose in testes was 100 mg/kg/day (2000 ppm). Drug related testicular atrophy and degeneration were observed in all treated groups as characterized by atrophy of seminiferous tubules (with spermatogenic arrest of primary and secondary spermatocytes) and vacuolization and condensation of nuclear material (especially evident for the spermatids). For ovaries, a decrease was noted in the numbers of primary follicles and increased degeneration of follicular epithelium on ovaries of the test group animals but are reported as minimal. The following frequency of cardiac focal infiltrations of leucocytes and occasional degenerative myocardial fibers were observed: control (1), 200 and 500 mg/kg (1 each), 300 and 400 mg/kg (3 each).

NEL: Not demonstrated

Comments: DT still agrees with the reviewer that the study is inadequate.

IV. THREE GENERATION REPRODUCTION & TERATOLOGY STUDY

Testing Laboratory: May & Baker, Dagenham, England

Compound: Dimetridazole

Species/Strain: Rats, Carworth Farms

Numbers: 20 females and 10 males per group

Dosage: Control 0, 100 ppm & 2000 ppm in diet

Matings: F_0, F_1a & b, F_2 a, b, c (c used for teratology) F_3 a, b

Methods: F_0 group fed 80 days prior to mating. All litters reduced to maximum of 8 pups on day 4

Results: One female in the 2000 ppm F_2b group was sacrificed before whelping because of a large mammary tumor

Lactation was poor in the F_2 a & b mating resulting in loss of several litters in each group. This effect was not noted in the F_0, F_1 and F_3 litters. Because of this it is not believed to be a toxicological problem. Teratology in the F_2c litters showed abnormalities in 0/213 controls, 4/217 100 ppm level and 1/239 at 2000 ppm.

Conclusions: No adverse effects were seen in either reproduction or teratology at 100 and 2000 ppm of the diet.

V. CHRONIC STUDIES

1. Dimetridazole, Chronic Study, 10 ppm in Rats, Testing Laboratory May & Baker, England

Review date: June 1, 1978

Reviewer: R. L. Gillespie, DVM

Species: Fifty per sex CFY rats as controls and 1 dose group at 10 ppm of the diet.

Length of Study: 128 weeks

Conduct of Study: Rats were weighed weekly, initially, then biweekly. Food consumption was recorded weekly. All animals were

weekly for [illegible]

At termination the following organs were weighed;

adrenals	brain
heart	kidneys
liver	lungs
pituitary	gonads

Histologic Exam.

adrenals	pancreas
pituitary	thyroid
liver	tumors
suspicious lesions	

Results: During the study, mortality seemed to be slightly higher in the 10 ppm males than in the controls. Total mortality prior to termination due to either death or in extremis sacrifice was 34/50 for the control and 44/50 for the 10 ppm group.

Over all drug intake averaged about 0.45 mg/kg/day for the males and 0.57 mg/kg/day for the females.

Tumor incidence:	Males		Females	
	Control	10 ppm	Control	10 ppm
Total in group:	50	50	50	50
# w/histology	34	40	47	47
# w/tumor-benign: or malignant	25	25	44	43
# w/malignant tumors:	11	14	8	11
# w/mammary-benign or malignant:	3	1	32	35
# w/malignant mammary tumors:	0	1	3	7
# w/malignant non-mammary tumors:	11	13	5	4

According to May & Baker Report none of these numbers is statistically significant. Based on a percentage of the animals with a histological report, the percentage of males with malignancies was 32.4% for the control and 35% for the treated. In the females it was 17% to 23% respectively. Total tumors did not show any appreciable difference.

The folowing tumor types were seen

	male control	10 ppm	female control	10 ppm
Adenocarcinoma	4	3	1	
Adenoma	3	1	6	3

arcinoma		1		
Fibroadenoma	16	14	2	1
Fibrosarcoma				
lemangioma		2		2
lemangiosarcoma				
lepatoma			1	1
.ipoma			1	2
.ymphoma	1	2	1	2
leoplas,m(not otherwise identified)			2	3
?habdomyosarcoma				2
arcoma		1	1	
Spindle cell sarcoma			2	6
lyxosarcoma	1		1	
'he@chromocytoma	1			
lalignant chromophate tumor	1		1	
.eydig cell tumor	1			
hromphobe adenoma	15	10	4	
ibroma	2	1	2	3

2. Dimetridazole Chronic Rat Study

Review Date	March 23, 1977
Reviewer:	R. L. Gillespie, DVM
Performing Lab:	May & Baker, Dagenham, England
No./Animals:	50/sex/dose level
Dosage Levels:	0, 100, 400 & 2000 ppm of diet

Mean Drug Intake:

Males	Females
100 ppm 3.8 mg/kg/day	4.6 mg/kg/day 4.6
400 ppm 15.1 mg/kg/day	18.3 mg/kg/day
2000 ppm 77.7 mg/kg/day	94.1 mg/kg/day

Observations: Food consumption and body weights noted. Hematology done terminally only. Starting at 20 weeks all rats were inspected and palpated weekly for tumors. Adrenals, brain, heart, kidneys, liver, lungs, pituitaries and gonads were weighed at terminal sacrifice.

Results: Other than tumors, few adverse effects were noted during the study. The high-dose females did not gain weight quite as well as the controls and lower dose groups, a less than 10% difference. Organ weights at termination were quite comparable.

Mortality was higher in the 2000 ppm males and the 400 and 2000 ppm females due to interim sacrifice for humane reasons because they were carrying large mammary tumors. Deaths from other causes were about equally

Males

	Deaths	Interim Sacrifice
Control	26	9
100 ppm	24	7
400 ppm	26	10
2000 ppm	23	17

Females

Deaths	Interim Sacrifice
16	11
19	10
14	18
14	29

Tumor Data: The first appearances of microscopically confirmed benign or malignant lesions were at 36 weeks in a high level female and at 43 weeks in a control male. These were both classified as malignant.

At 78 weeks total tumor incidence was as follows:

	Males	Females
0	6	7
100	3	3
400	1	2
2000	3	15

At 104 weeks, it was as follows:

	Males	Females
0	15	21
100	10	20
400	12	23
2000	18	33

At 122 weeks, it was as follows:

	Males	Females
0	24	40
100	28	33
400	22	42
2000	29	43

Please note the 122 week data include animals in which lesions were found only at terminal kill such as pituitary adenomas.

Confirmed malignancies at 78 weeks

	Males	Females
Control	2	2
100	1	2
400	0	0
2000	1	4

At 104 weeks the results were:

	Males	Females
Control	4	5
100	6	5
400	3	6
2000	4	7

At terminal sacrifice the results were:

	Males	Females
Control	9	6
100	7	9
400	5	10
2000	6	11

The summary provided by the petitioner included pituitary lesions, such as chromophobe adenomas which, of course, were listed as benign lesions.

After consultation with Dr. Monlux (HFF-134) and Dr. Singh of our staff, is was concluded that since these are spontaneous lesions common to all aging rats and are discovered only at terminal autopsy, these could be removed from consideration. Both Drs. Singh and Monlux emphasized that this could hold only if the incidence was no greater than the non-medicated controls which was true in this instance.

The following is a summary of the lesions (less pituitary adenomas) in the animals on which histological evaluation is available. Some few were lost to autolysis and/or cannibalism.

MALES

	C	L	M	H
No. of animals examined	42	44	45	43
No of animals w/benign lesions:	10	13	8	18
No of animals w/ malignant lesions:	8	7	5	7
No. of animals w/non-mammary benign lesions:	7	8	7	3
No. of animals w/ non-mammary malignant lesions:	7	6	5	4
No. of animals w/mammary benign lesions:	3	5	1	15

[illegible]

malignant lesions:	1	1	0	3
Total of mammary benign and malignant lesions:	4	6	1	18

FEMALES

	C	L	M	H
No. of animals examined	44	40	43	47
No. of animals w/ benign lesions:	28	19	32	31
No. of animals w/ malignant lesions:	6	9	10	11
No. of animals w/non-mammary benign lesions:	2	2	3	0
No. of animals w/ malignant non-mammary lesions:	3	5	4	6
No. of animals w/ benign mammary lesions:	28	20	31	33
No. of animals w/ malignant mammary lesions:	3	4	6	5
Total of mammary lesions benign and malignant:	31	24	37	38

re are the various tumor types, numbers and sites seen in this study.

Males

	Control	100 ppm	400 ppm	2000 ppm
renal				
enocarcinoma				
rtical adenoma	1	1	2	1
dullary adenoma	3	2		
adder				
ansitional cell tumor (malignant)				
lon	1			
e				
nexal carcinoma		1		
bcutaneous Tissue				
broma	1	3	1	4
brosarcoma/sarcoma	2		2	1
poma/Fibrolipoma	1			2
oosarcoma	1	2		
ver				

ımphangıol.povy				
ırenchymal cell adenoma	1			
ıng				
lenoma			1	1
ɜnign cystic papilloma				
ʼonchial carcinoma	1			
ןuamous cell carcinoma			1	
ımphoid Tissue				
ımphosarcoma/malignant lymphoma	3	2	1	2
ımmary				
lenocarcinoma/carcinoma	1	1		1
lenoma/fibroadenoma	2		1	6
ibrosarcoma/sarcoma				2
ibroma	3	3	1	9
ɜninges				
ɜningioma			2	1
ɜrve				
ɜurilemmoma	1			
ıary				
Granulosa cell tumor				
Pancreas				
Islet cell adenoma	1	1	1	1
Parathyroid				
Adenoma	1	1	1	1
Pituitary				
Chromophobadenoma	8	11	11	9
Skin				
Angioma				
Basal cell papilloma		1		2
Basisquamous tumor (malignant)				1
Squamous cell carcinoma	1	1	1	1
Site unknown				
Spindle cell sarcoma		1		
Testes				
Leydig cell tumor	1			
Reticulum				
Reticulosis generalized				
Thyroid				

ioma	3	2		1
estomach				
amous papilloma				

Females

	Control	100 ppm	400 ppm	2000 ppm
enal				
nocarcinoma			1	1
tical adenoma	1		1	1
ullary adenoma		2		1
dder				
nsitional cell tumor (malignant)		1		
on				
nocarcinoma				
exal carcinoma				
cutaneous tissue				
roma			1	2
rosarcoma/sarcoma			3	
oma/Fibrolipoma	3			
osarcoma				
ver				
jioma		1		1
mphangiolipoma				1
renchymal cell adenoma	1		1	
ng				
enoma			1	
nign cystic papilloma	1			
onchial carcinoma				
uamous cell carcinoma				
mphosarcoma/malignant lymphoma	1	1	3	2
mmary				
enocarcinoma/carcinoma	2	2	4	2
enoma/fibroadenoma	27	23	31	35
broma	3	3	7	14
brosarcoma/sarcoma	1	2		3
ninges				
ningioma				
rve				

vary				
ranulosa cell tumor			1	
ancreas				
slet cell adenoma		2		
arathyroid				
denoma	2			1
ituitary				
hromophobe adenoma	20	14	14	11
kin				
ngioma	1			
asal cell papilloma				1 c
asisquamous tumor (malignant)				
quamous cell carcinoma		2		1
ite unknown				
pindle cell sarcoma	2			
ecticulum				
eticulosis generalized				1
hyroid				
denocarcinoma				
denoma	2	2	3	1
terus				
ervical fibroma				
ibrosarcoma				1
currous adenocarcinoma		1		
quamous cell carcinoma		1		
orestomach				
quamous papilloma				

Background Colony
Data:

hese were from 2 control groups of rats of the same source although not un concurrently with the Dimetridazole study.

Total malignancies

Males	Females
14/117	19/121

Mammary gland malignancies

ales Females

/117 2/121

hese animals were all sacrificed at 104 weeks.

Conclusions:

[illegible])

While there was a slight increase in malignancies in the treated females from 6 in the control to 11 in the high dose group, it was not statistically significant. However, there was a statistically significant increase in benign neoplasms in the mid and high dose females and in the high dose males.

On the basis of this study the drug is classified as a benign tumorigen.

3. Dimetridazole Tumorigenicity

Testing Laboratory University of Wisconsin

Review Date: April 11, 1971

Reviewer:

[illegible]

Species:
ague Dawley female rats

Method:
rty-five female rats averaging 54 grams in weight at the start of the t were fed dimetridazole at a level of 0.25% in the diet for 46 weeks then maintained on a control diet for an additional 20 weeks. Thirty ales were maintained as non-medicated controls.

At death or terminal sacrifice the following tissues were taken for histology:

urinary bladder
liver
spleen
kidneys
uterus
mammary tissue
lumbar vertebrae

heart
lung
adrenals
G. I tract
ovaries
chest wall
tumors

Observations: Growth and food consumption were essentially similar. At termination the treated group weight averaged about 10 grams less than the controls. Survival was good up to 40 weeks at which time mortality increased in the treated group. At termination there were 22/30 (73%) survivors in the control and 18/35 (54%) in the treated group.

Tumor Development: Treated rats

33 weeks	1 rat
45 weeks	9 rats
55 weeks	16 rats
66 weeks	25 rats

Control rats

41 weeks	1 rat
66 weeks	4 rats

Histopathology: All tumors in both groups were classified as fibroadenomas. Three of the treated rats had transitional cell hyperplasia of the kidneys.

MUTAGENICITY STUDIES

Salmonella

a. Reference: C.Y. Wang, et al (1975) Cancer Res. 35:3611

Procedure: Spot Test using TA98 and TA100 without activation. Dimetridazole was dissolved in DMSO and [illegible]

Toxicity were recorded

Results: There was no detectable toxicity in either strain at any dose. Positive mutagenicity was detected in TA98 at 80 ug/plate and TA-100 at 5 and 80 ug/plate.

Reference: H.S. Rosenkranz, et.al. (1976) Mutat. Res. 38:203

Procedure: Plate incorporation assay using TA100 without activation. Dimetridazole was dissolved in DMSO and tested at 25 and 250 ug/plate.

Results: Positive mutagenicity was recorded at both 25 and 250 ug/plate.

Reference: D. G. Lindmark & M. Muller (1976). Antimicrobial Agents & Chemotherapy 10:476.

Procedure: Plate incorporation test using TA100 and TA100-FR (Deficient in nitroreductase). Dimetridazole was tested at 10-500 ug/ml (1-50 ug/plate). Neither solvent nor number of doses were specified. The main purpose of this study was to determine the nitroreductase contribution to mutagenicity. Tests were conducted both aerobically and anaerobically.

Results: Positive mutagenicity results were recorded with TA100 both aerobically and anaerobically and with TA100-FR only anaerobically which indicated the requirement for nitroreduction. Only summary data were reported, so it was not possible to determine the lowest effective dose.

Reference: C.E. Voogd, et.al. (1979) Mutat. Res. 66:207

Procedure: Plate incorporation assay using TA100 without activation was conducted. Dimetridazole was dissolved in DMSO and tested at .02, .05, .1, .2, .5 and [illegible] mmol/l. (Calculations by reviewer Indicate that [illegible] corresponds To

Results: Positive mutagenicity results were recorded at 0.05 mmol/l and all higher doses. There was no evidence of toxicity (ie. reduced number of revertants) even at the highest dose.

Other Bacteria:

a. Reference: C.E. Voogd, et.al. (1974) Mutat. Res. 26:483

b. Procedure: The Luria and Delbruck Fluctuation test was performed using (i) Klebsiella pneumoniae, (ii) Escherichia coli K-12 and (iii) Citrobacter freundii 425 without metabolic activation. Dimetridazole was tested at .01, .025, .05, .1, .25 and .5 mM. Both mutant counts and cell number were determined so that the mutation frequency could be calculated.

Results: Positive mutagenicity results were recorded in all three species. Since minimal criteria for a positive were not provided, the lowest effective dose cannot be determined. The highest dose mutation frequency was 15 to 17 times the control rate in all three species.

c. Reference: C.E. Voogd, et.al. (1979) Mutat Res. 66:207

Procedure: Fluctuation test in Klebsiella was conducted as above. Concentrations of dimetridazole used were .02, .05, .1, .2, .5 and 1 mmol/l.

Results: Positive mutagenicity results were recorded. The increase in mutation frequency at 0.5 mmol/l was 17 fold in this study and 15 fold in the previous study.

Yeast:

Reference: C.E. Voogd, et.al. (1980) Mutat. Res. 78:233

Procedure: Mitotic gene conversion assay was performed using Saccharomyces strain D-4. Dimetridazole was added to the growth media at various (not specified) concentrations and cells were incubated for 45 hrs. at 30°C. Mitotic gene convertants were recorded at the highest concentration at which cell multiplication occurred (0.05% w/v in the media).

Results: There was little toxicity at this concentration. A positive mutagenic [illegible] a tenfold increase in gene conversion.

hila:

eference: P.G. Kramers (1978) Mutat. Res. 53:213 (Abstract)

rocedure: The sex-linked recessive lethal test was conducted. Adult males of the Oregon K strain were tested and mated to Basc females. The dose of dimetridazole was not reported.

Results: The author stated that the results were "borderline" for dimetridazole

Comments: Since this was an abstract and no data was reported this is considered an unacceptable study.

eduled DNA synthesis in rat hepatocytes

Reference: G.S. Probst, et.al. (1981) Environmental Mutagenesis 3:11.

Procedure: Hepatocytes were obtained from male Fisher 344 rats, attached to coverslips and exposed for 5 hrs. to test agent. Dimetridazole was dissolved in DMSO. Eight concentrations ranging from 0.5 to 1,000 nmol/ml were tested. Subsequent to staining and developing the silver grains over 20 nuclei were counted. Silver grains over three "nucleus-size" cytoplasmic areas were counted per nucleus to establish background counts (these were subtracted from nuclear counts).

Results: Dimetridazole was reported negative with 5 hrs. exposure (no data presented-only footnoted). The experiment was repeated with a 20 hr. exposure and only the results from the highest dose (1,000 nmol/ml) were reported. The mean nuclear count for dimetridazole treatment was 0.3 ± 1.2 and the control was 0.0 ± 1.6.

Comments: This is an apparent negative result but the counts for other doses were not recorded and there was no means of detecting toxicity reported. Hence, it cannot be concluded that a negative finding was demonstrated.

Micronucleus Test

Reference: J. L. Oud. et.al. (1979) Mutat. Res. 68:179

Procedure: Swiss RIV mice were injected ip with 50

DMSO at a dose [illegible] mg/kg [illegible]
Ten animals (5 males, 5 females) were injected. Equal numbers of mice were injected with 50% DMSO to serve as controls. Mice were sacrificed 24 hrs after injection and bone marrow smears were prepared and stained. Micronucleated cells were scored from 1000 polychromatic erythrocytes per animal.

Results: The mean number of micronuclei/1000 cells was 3.6 for the dimetridazole group and 2.6 for controls. The ranges were 0-6 and 1-5, respectively.

Comments: This study cannot be accepted as an adequate demonstration of a negative result because: (i) only a single dose was used, and (ii) only a single injection was used. Current practice for this assay employs two injections, 30 and 6 hrs. before sacrifice and several doses including the MTD.

Conclusions: Dimetridazole has been demonstrated to be mutagenic in a range of bacterial test systems and to induce mitotic gene conversion in yeast. The in vivo Drosophila and mouse tests and the UDS test were all inadequate for a definitive conclusion.

URRENT STATUS

ialsbury has indicated a willingness to conduct radiotracer studies in urkeys, but we suggested they wait until we had made a final ietermination of the necessary level of method sensitivity.

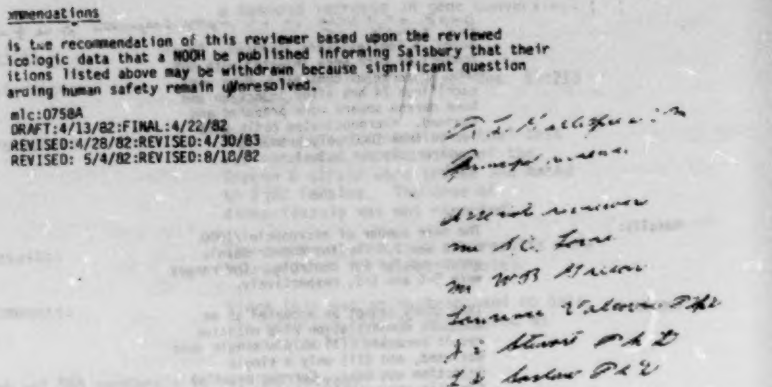
le had asked for a study in a second rodent species such as the mouse to nake a final determination as to potential carcinogenicity. Once that vas completed and reviewed, we could use the S.O.M. guidelines to ietermine an acceptable level of residue. This was communicated to Hess Clark and Salsbury Laboratories in a conference August 23, 1978 attended y these two companies and May & Baker from England who supplies this irug. We reemphasized the need for the mouse study and advised them that vithout it, Salsbury Laboratories approvals were in jeopardy.

It is our understanding that May and Baker have refused to do the mouse study requested so we have reached an impasse.

ummary

The two rat studies we have indicates that the product is definitely a umorigen. In the May & Baker study, the longer of the two, carcinoma vere 6, 9, 9 and 11 (control to high dose respectively). These are not statistically significant but there is a trend. In the May & Baker study ther was an increase in male fibroadenomas of the mammary gland. (THE [illegible] visconsin study did not use males). Several of the short term tests also indicate evidence of mutagenicity.

In the absence of a study in another species, we cannot conclude what is safe dose whether using SOM or any other method.



mmendations

is the recommendation of this reviewer based upon the reviewed
icologic data that a NOOH be published informing Salsbury that their
itions listed above may be withdrawn because significant question
arding human safety remain unresolved.

mlc:0758A
DRAFT:4/13/82:FINAL:4/22/82
REVISED:4/28/82:REVISED:4/30/83
REVISED: 5/4/82:REVISED:8/18/82

Mr. **Weiss**. In the 3 years since this recommendation was made, has FDA at least initiated proceedings to remove dimetridazole from the market?

Dr. **Crawford**. We have not. It is in the same class of drugs, as you may know, with ipronidazole that we just mentioned, and it is now being considered for appropriate action. Also in that class is an approved drug for humans called metromidazole. So we are considering them all in their totality. They have the same toxicological profile. The warnings on the human drug are deemed to be sufficient because—these are useful drugs. And one way to try to deal with them is either to develop a method or to label them for use in drugs other than food-producing animals or a variety of strategies. Ultimately, it is the feeling of many scientists that these products will have to come off the market. We are considering that now in terms of a list of several drugs that these questions have been raised about.

Mr. **Weiss**. Is there at present an acceptable and practicable method of detecting dimetridazole residues in edible animal tissue?

Dr. **Crawford**. I believe there is a method that is used by USDA for turkeys that may not be effective and is—in detecting all the metabolites and all the various other aspects of the use of the drug. So if you look at the USDA list, I believe you will see that method mentioned.

As Mr. Dols pointed out, there is some question about how effective this method is.

Mr. **Weiss**. Mr. Dols, do you want to comment on that? Is there at present an acceptable and practicable method for detecting dimetridazole residues in edible animal tissue?

Mr. **Dols**. No, there is not, for enforcing the established tolerance.

Mr. **Weiss**. Since FDA has no way to assure that the public is not being exposed to "unsafe" levels of that drug in its food supply, on what basis has FDA permitted its continued marketing?

Dr. **Crawford**. Well, we have attempted to gather together the literature on the subject, the scientific literature, and be sure just what the actual risks are. And, as you mentioned, from the memos that you have at the present time, it does appear that these substances must be considered for administrative action, and so we are now getting around to it.

One of the things that we have pointed out before is that it is a long involved process to get drugs off the market once they're on, and much less of a process is involved in approving them to go on the market.

Now, all these that we've mentioned, dimetridazole, ipronidazole, metronidazole, were approved a number of years ago and we frequently refer to whether or not a drug can meet 1985 standards; 1965 standards, Mr. Chairman, and 1985 standards are quite different. And we have to, from time to time, review the drugs and see if they are consistent with safety requirements now, and that is what we are doing. As you correctly point out, there are questions about the continued approvability of these three.

Mr. **Weiss.** I thought you were very eloquent in pointing out why some of these animal drugs are really more dangerous to human health than human drugs. Here you have a recommendation made almost 3 years ago by one of your people, Dr. Gillespie, to begin proceedings to remove the drug from the market. There is no way at this point of adequately determining what the drug's residues are. Although there is no way that people can tell what damage the drug is causing them, we know that it is a potential carcinogen. Yet no steps have been taken to remove it from the market. I would think that contradicts the very genuine concerns that you earlier expressed.

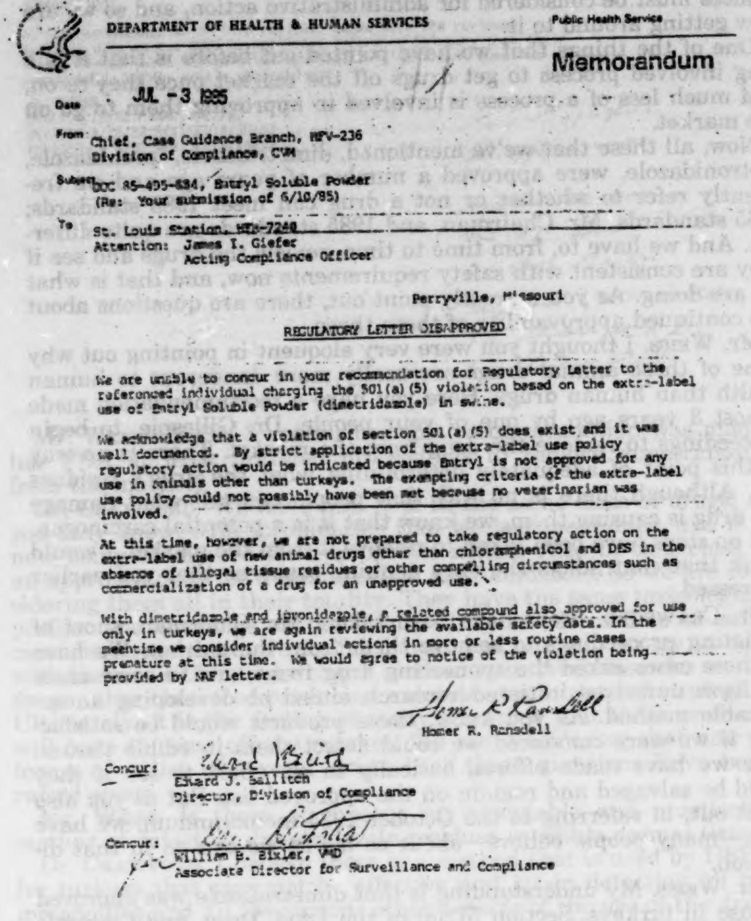
Dr. **Crawford.** Steps have been taken, Mr. Chairman, short of initiating proceedings to remove them from the market. We have in these cases asked the sponsoring drug firms, and in some cases we have ourselves initiated research aimed at developing an acceptable method. As you know, these products would be satisfactory if we were convinced we could detect them in edible tissues.

So we have made efforts, basically in an effort to see if they could be salvaged and remain on the approved list. But as you also point out, in referring to the October 1984 memorandum, we have gone—many people believe—about as far as we can go in that direction.

Mr. **Weiss.** My understanding is that dimetridazole was approved for use in turkeys. Section 512(a) of the Food, Drug, and Cosmetic Act prohibits the unapproved use of any new animal drug. This section would prohibit its use in species for which it has not been approved.

Why, therefore, did CVM on July 3, 1985, disapprove the recommendation of FDA's St. Louis Station to issue a regulatory letter to a Missouri hog feeding operation for illegally using dimetridazole in swine, an unapproved species?

[Documents concerning this case follow:]



DEPARTMENT OF HEALTH & HUMAN SERVICES　　Public Health Service

Memorandum

Date　JUL -3 1985

From　Chief, Case Guidance Branch, HFV-236
Division of Compliance, CVM

Subject　DOC 85-495-634, Entryl Soluble Powder
(Re: Your submission of 6/10/85)

To　St. Louis Station, HFR-7240
Attention: James I. Giefer
Acting Compliance Officer

Perryville, Missouri

REGULATORY LETTER DISAPPROVED

We are unable to concur in your recommendation for Regulatory Letter to the referenced individual charging the 501(a)(5) violation based on the extra-label use of Emtryl Soluble Powder (dimetridazole) in swine.

We acknowledge that a violation of section 501(a)(5) does exist and it was well documented. By strict application of the extra-label use policy regulatory action would be indicated because Emtryl is not approved for any use in animals other than turkeys. The exempting criteria of the extra-label use policy could not possibly have been met because no veterinarian was involved.

At this time, however, we are not prepared to take regulatory action on the extra-label use of new animal drugs other than chloramphenicol and DES in the absence of illegal tissue residues or other compelling circumstances such as commercialization of a drug for an unapproved use.

With dimetridazole and ipronidazole, a related compound also approved for use only in turkeys, we are again reviewing the available safety data. In the meantime we consider individual actions in more or less routine cases premature at this time. We would agree to notice of the violation being provided by NAF letter.

Homer R. Ransdell

Homer R. Ransdell

Concur:
Edward J. Ballitch
Director, Division of Compliance

Concur:
William B. Bixler, VMD
Associate Director for Surveillance and Compliance

cc: HFR-7200
HFC-102
HFC-214
HFV-1
HFV-200
HFV-230
HFV-230
HFV-236 (HR/RL 5-159)
~~HFA-224~~

DDEAN:6/28/85:dp:7/1/85draft
DDEAN:7/1/85:dp:7/1/85final

Diane

DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION, REGION VII

Memorandum

Date June 10, 1985

From St. Louis Station/HFR-7240
Compliance Branch

Subject Regulatory Letter Recommendation Re: President
DOC 85-495-884 Emtryl Soluble Powder

To

Center for Veterinary Medicine Perryville, MO 63775
Case Guidance Branch/HFV-236

REGULATORY LETTER RECOMMENDATION

We recommend issuance of a regulatory letter to charging 501(a)(5) regarding his extra-label use of Emtryl Soluble Powder for the treatment of bloody scours in swine which resulted in his adulteration of the veterinary drug. This product which in itself is a new drug became unsafe within the meaning of Section 512 in that its use in food producing animals did not conform to its approval.

. operates primarily as a manufacturer of commercial feeds and secondarily as a custom formula mixer. The firm has also begun contract hog feeding operations in Missouri and Illinois. In this latter venture buys the pigs and supplies the feeds. The contracted farmer is responsible for the daily care of the pigs and also is paid for rent of the facilities. , has nine currently active contracts, one of which is with himself. The sale of Emtryl Soluble Powder from . to (contract No. 47) for use for bloody scours in swine serves as the basis for this regulatory letter recommendation.

St. Louis Station initiated an inspection of , on February 6, 1985 (tab 1). Information regarding the contract hog feed operations was obtained. Basically buys feeder pigs and supplies all the feeds. The farmer, who owns the confinement facility, is responsible for the daily care of the pigs. All hogs are hedged in an attempt to lock in a profit and if a profit is realized the farmer is paid for his labor and the rent of the facilities (See tab 1, page 1, paragraph 6).

The nine active contract hog feeding operations were identified and one of these was Contract No. 47 for (See tab 1, page 3, paragraph 2). The feeding program for pigs on contract was obtained (See tab 1, page 3, paragraph 4).

A review of invoices for these hog feeding contracts found sales of Emtryl Soluble Powder to Contract No. 47 - as well as sales of LS-50 Water Soluble (lincomycin - spectinomycin) to several contracts (See tab 1, page 3, paragraph 5 and page 4, paragraph 1). Concerning the sale of Emtryl

5-159
6-14-85

Soluble Powder to . David Danker, the manager of , stated that the drug was used in an effort to control a problem of bloody scours which developed in the group of hogs being fed under contract with (See tab 1, page 4, paragraph 3). Regarding the sales of LS-50 Water Soluble (lincomycin - spectinomycin) to several contracts it was reported that the drug was being used as a treatment for Microplasma Shock Syndrome (Gut Edema) in swine (See tab 1, page 4, paragraph 1).

The extra-label use of Emtryl Soluble Powder did not involve any veterinarian-client-patient relationship. A follow-up inspection was made at on March 7, 1985 to collect documentary samples of extra-label use of Emtryl Soluble Powder and LS-50 Water Soluble (lincomycin - spectinomycin). Sales of Emtryl Soluble Powder from . to were documented under DOC 85-495-884 (tab 2). In the affidavit for that sample David M. Danker, Manager for ., stated that Emtryl Soluble Powder was used by area farmers to treat bloody scours in swine. Mr. Danker added that the documented sales were used to water medicate hogs being fed by .

However, the use of LS-50 Water Soluble (lincomycin - spectinomycin) was under the direction of the firm's consulting veterinarian, Dr. Ben Ellis, DVM (See tab 1, page 4, paragraph 1). Also LS-50 was used in approximately 3 to 5% of the pigs purchased for contract feeding. The drug was used in pigs which were not thrifty and more susceptible to disease (See tab 1, page 4, paragraph 2).

A follow-up investigation was made at Dr. Ben Ellis, DVM on March 7, 1984 (tab 3). That investigation confirmed that Dr. Ellis was the consulting veterinarian to . and that he does periodically visit hog confinement units and is familiar with the pigs being placed on feed. Dr. Ellis confirmed that he recommended the use of LS-50 for injection into pigs and that he felt there was no withdrawal problems associated with the extra-label use of this drug. Consequently our recommendation does not include the extra-label use of LS-50 Water Soluble (lincomycin - spectinomycin). We are including in our draft regulatory letter recommendation information on the extra-label use policy. With regard to the extra-label use of LS-50 we are advising that controls are needed to assure that the identity of the treated animals must be carefully maintained and that a significantly extended time period be assigned for drug withdrawal prior to marketing and that steps be taken to assure that the assigned time frames are met and no illegal residues occur.

Our draft regulatory letter also contains an information section on observed deviations from the Good Manufacturing Practices regulations for medicated feeds. That section is self explanatory.

Based on the above we recommend issuance of a regulatory letter charging 501(a)(5).

James I. Giefer
James I. Giefer
Acting Compliance Officer

Raymond K. Hedblad
Raymond K. Hedblad - Concur
Chief
St. Louis Station

JIG/RKH/sp

Encls: Draft Regulatory Letter
Tab 1 EIR 2/6-8 & 11-12/85
Tab 2 DOC 85-495-884
Tab 3 Cook/Bringman memo dated 3/8/85

cc: HFA-224; JAA; FSIA; S/J; F/J; JIG; SLS; R/F

<DATE>

DRAFT REGULATORY LETTER

Certified Mail - Return Receipt Requested

, President

Perryville, MO 63775

85-STL-

Dear Mr.

During inspections of your facility on February 6-8, & 11-12, 1985 and March 7, 1985 our investigator observed a serious violation of the Federal Food, Drug and Cosmetic Act as follows:

Section	Brief Description
501(a)(5)	The veterinary drug, Emtryl Soluble Powder, is a new animal drug which became unsafe within the meaning of Section 512 in that the use or intended use of this drug in food producing animals does not conform to its approval.

We request that you take prompt action to correct this violation. If such action is not taken, the Food and Drug Administration is prepared to invoke regulatory sanctions such as seizure and/or injunction.

Extra-label use of drugs in treating food-producing animals may be considered only in special circumstances. We would not ordinarily consider taking regulatory action against your extra-label use of drug products provided all of the following criteria are met and precautions observed:

1. a careful medical diagnosis is made by an attending veterinarian within the context of a valid veterinarian-client-patient relationship as defined by the American Veterinary Medical Association;

2. a determination is made that, (a) there is no marketed drug specifically labeled to treat the condition diagnosed, or (b) drug therapy at the dosage recommended by the labeling has been found clinically ineffective in the animals to be treated;

3. procedures are instituted to assure that identity of the treated animals is carefully maintained; and

4. significantly extended time period is assigned for withdrawal prior to marketing meat, milk, or eggs; steps are taken to assure that the assigned timeframes are met, and no illegal residues occur.

None of the above "exempting" criteria were met in your use of Emtryl Soluble Powder in the treatment of bloody scours in swine. Furthermore, the above "exempting" criteria do not include drug use in treating food-producing animals by the layman. Lay persons cannot be expected to have sufficient knowledge and understanding concerning animal diseases, pharmacology, toxicology, drug interactions, and other scientific parameters to use drugs in treating food-producing animals in any way other than as labeled.

Additionally your extra-label use of the veterinary drug, LS-50 Water Soluble (lincomycin - spectinomycin), for the treatment of Microplasma Shock Syndrome (Gut Edema) in swine needs to be further controlled to assure that the identity of the treated animals is carefully maintained and that a significantly extended time period is assigned for drug withdrawal prior to marketing and that steps are taken to assure that the assigned timeframes are met and no illegal residues occur.

Also regarding your medicated feed manufacturing operations, our investigator observed deviations from the Current Good Manufacturing Practices regulations as set forth in Part 225 Title 21 Code of Federal Regulations (21 CFR Part 225). Section 501(a)(2)(B) of the Act requires that the methods used in or the facilities or controls used for the manufacture, processing, packing or holding of medicated feeds conform with the requirements of 21 CFR Part 225. Deviations from 21 CFR Part 225 were observed during our February 6-8 & 11-12; 1985 inspection and were listed on form FD-483, Inspectional Observations, issued to David M. Danker, Manager, at the conclusion of the inspection. A copy of the form FD-483 was sent to you on February 13, 1985. That list is not intended to be all inclusive of deficiencies that may exist in your operation, as the form FD-483 contains only those which were observed during the inspection.

One observation on the form FD-483 concerned improper sequencing of feeds. A batch of Ground Corn was the first feed manufactured on February 2, 1985 which followed a Carbadox medicated swine feed which was the last batch manufactured on February 1, 1985. An analysis of a sample of the Ground Corn found Carbadox contamination. As president of it is your responsibility to correct the deviations cited and to assure your firm's compliance with the Federal Food, Drug and Cosmetic Act.

Please advise us in writing within ten (10) days of the receipt of this letter, delineating the steps you have taken or intend to take, to correct these violations. Your response should be directed to James I. Giefer, Acting Compliance Officer, at the address referenced in the letterhead.

Sincerely,

Raymond K. Hedblad
Chief
St. Louis Station

JIG/RKH/sp

bcc: HFA-224; JAA; FSIA; S/J; F/J; SLS; JIG; R/F

Dr. **Crawford**. It could have been the quality of the case. I'm not sure.

Perhaps Mr. Shane could comment on that.

Mr. **Weiss**. Please.

Mr. **Shane**. The question that was involved in dealing with the clinic was one of involvement in the practice of veterinary medicine.

Mr. **Weiss**. Mr. Shane, I don't think this refers to a clinic but a hog feeding——

Mr. **Shane**. No; Hartley Veterinary Clinic in Hartley, Iowa. That's——

Mr. **Weiss**. No, no; the hog feeding operation in Perryfield, MO.

Mr. **Shane**. I'm sorry, but I don't have that case with me. I have not seen the turn-down on it. If I could see that, please?

Mr. **Weiss**. Yes.

While you are waiting to look at that, let me continue. In its July 3, 1985, disapproval notice, CVM wrote, "At this time, however, we are not prepared to take regulatory action on the extra-label use of new animal drugs other than——"

Mr. **Shane**. Chloramphenicol.

Mr. **Weiss** [continuing]. "Chloramphenicol and DES in the absence of illegal tissue residues or other compelling circumstances such as commercialization of a drug for an unapproved use." Dr. Crawford, don't you think that the illegal use of a potentially carcinogenic drug, in an unapproved species is a "compelling circumstance" worthy of regulatory action from the Food and Drug Administration?

Dr. **Crawford**. Yes. I am not familiar with that case, either. Perhaps I could look at it.

Mr. **Weiss**. Since we are going to continue the hearings tomorrow, perhaps you can review that case today in preparation for questions about it.

Dr. **Crawford**. I will confer with the people involved in the process.

Mr. **Weiss**. On March 10, 1983, CVM advised a company seeking to study the use of dimetridazole in swine:

"Dimetridazole is a suspect carcinogen, so until the human food safety issues with respect to metabolites, target tissues, drug depletion rates, and analytical methodology are sufficiently resolved, we do not consider clinical trials in swine to be appropriate."

[The March 10, 1983, letter to this company follows:]

Chron.
[illegible]

March 10, 1983

Dr. Irving S. Rossoff
Illinois Antibiotics Co.
515 Springfield Road
P. O. Box 333
Taylorville, Illinois 62568

Dear Dr. Rossoff:

This is in response to your letter of November 23, 1982, regarding dimetridazole.

As you know, dimetridazole is approved only for treating turkeys through feed or drinking water. It may not be legally used in treating swine in the United States.

The investigational exemption provisions of the Federal Food, Drug and Cosmetic Act and the regulations in 21 CFR 511.1 may not serve as the basis for general use of a drug. Clinical investigations and human food safety studies are carefully structured, critically performed and closely monitored on limited numbers of clinical and laboratory animals. Dimetridazole is a suspected carcinogen, so until the human food safety issues with respect to metabolites, target tissues, drug depletion rates and analytical methodology are sufficiently resolved, we do not consider clinical trials in swine to be appropriate. You may conduct the appropriate human food studies, and we will be pleased to discuss this with you in detail. Since very small quantities of dimetridazole would be needed for human food safety studies, import would be limited to the quantity needed for your laboratory and target species studies.

If you wish to pursue human food safety studies, we suggest that you schedule a meeting through my office. The enclosed FEDERAL REGISTER notices and guideline will be helpful in the pursuit of these studies.

Sincerely yours,

Robert A. Baldwin, D.V.M.
Associate Director for Scientific Evaluation
Bureau of Veterinary Medicine

Enclosures

cc: HFV-230;HFV-100
HFV-301;HFV-130
HFV-133;HFV-200
HFR-5100
EBallitch:km

Mr. **Weiss**. If this drug may not even be used in limited clinical studies in swine, why does FDA not act against those who illegally add it to the Nation's edible pork supply? In one instance you prohibit someone seeking to use it on a limited study basis, because you have all kinds of safety problems with it. In another instance, you reject your St. Louis Station's recommendation that you crack down on someone using it illegally.

Dr. **Crawford**. When I returned to FDA in 1982, we had this request to use it experimentally. I think that probably is not the first one of those in swine, which, as you pointed out, we rejected.

Mr. **Weiss**. And, to your knowledge, has FDA taken steps since then to eliminate its illegal use in swine?

Dr. **Crawford**. We have generally cautioned against its use and we have informed the field that it is on a list of products to be reviewed. As was also pointed out earlier, we have placed it not in the same category of chloramphenicol. We believe the risk is greater with chloramphenicol. So field forces have been informed to concentrate on that drug. This one will be one that now would be eligible to fit in the same category, though.

Mr. **Weiss**. A July 12, 1984, memorandum from FDA's Kansas City Compliance Branch—I suppose that would be your branch, Mr. Shane——

Mr. **Shane**. Yes.

Mr. **Weiss** [continuing]. States that misuse of dimetridazole in swine represents an "extensive," apparently "industry-wide" problem that "has gone on for years."

[The memorandum referred to follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION, REGION VII

Log to Judy

Memorandum

Date July 12, 1984

Professional Agricultural
Supply, Inc., (Pro Ag)
Wichita, KS

From Kansas City District
Compliance Branch/HFR-7140

Subject DOC 84-352-730, DOC 84-353-186/188/189 - Entrymix
DOC 84-352-812 - Carbadox
DOC 84-352-813 - Liquamycin

To CENTER FOR VETERINARY MEDICINE
CASE GUIDANCE BRANCH/HFV-236

PROPOSED REGULATORY LETTER

Inspection of this firm 2/14-17/84 disclosed widespread distribution of chloramphenicol for use in food producing animals. Quantities of this drug were seized in firm's possession 5/25/84, District of Kansas, 84-1321-K, FDC 64256. The drug was adulterated under 501(a)(5). The inspection also disclosed the distribution of FD-1800 requiring premixes to persons not entitled to receive same and the distribution of Rx veterinary drugs to persons who did not hold prescriptions. This includes chloramphenicol.

Concurrently with processing of the seizure, KAN-DO made follow-up investigations into the firm's premix and Rx vet drug sales violations. We have documented violations and believe the firm should be placed on formal warning via a Regulatory Letter. While the seizure was based on a 501(a)(5) charge, the circumstances in their premix distribution are different. Although chloramphenicol is Rx and was distributed without a veterinarian's order, we did not charge 502(f)(1) in the seizure action.

Our 6/6-8/84 EI was to check on firm's chloramphenicol distribution since 4/1/84. All May, 1984 invoices were reviewed. No improper distribution was noted. Only one possible illegal sale of an Rx drug was noted. Sales of Entrymix to non-FD-1800 holders were noted and Gordon L. Raspberry, DVM, President, stated he was unaware Entrymix required an FD-1800. A follow-up at Salsbury Labs, the manufacturer of Entrymix, showed Pro Ag has signed agreements to meet the requirements of 21 CFR 510.7 in their distribution of Entrymix. In two instances, these forms were signed by Dr. Raspberry.

[illegible] The [illegible]

Referenced samples are explained as follows:

1. DOC 84-352-812 was collected following our 2/84 EI to show the improper distribution of Mecadox 10. KS signed an affidavit that he did not hold approval to use this premix. He placed the order via telephone with Pro Ag and the person filling the order did not ask if he held FD-1800 approval.

1

RL 4-163
7-16-84

2. DOC 84-352-813 was collected to show the sale of Liquamycin LA-200 without a prescription. Sawyer, KS signed an affidavit attesting he did not have nor was he asked for a prescription prior to the sale. Numerous sales of chloramphenicol were made without prescriptions prior to our February 1984 inspection. Such a sale was documented and formed the basis of our Regulatory Letter to Wells Bros. Dairy, Wichita, KS (DOC 84-352-809). Since our review of May, 1984 invoices showed only one possible illegal sale, you may deem the inspectional warning adequate and choose not to include the 502(f)(1) charge in the Regulatory Letter. We prefer it remain, however.

3. DOC 84-353-186 represents stock of Emtrymix on hand at Pro Ag and shows its interstate origin. In the affidavit attached to it, Dr. Raspberry states the firm did not determine if Emtrymix consignees held FD-1800 approval prior to shipment.

4. DOC 84-353-188 represents Emtrymix sold to Carp Bros., Wichita, KS. stated in an affidavit the drug is used to treat hogs for dysentary and that they do not hold FD-1800 approval for the drug. NOTE: It is a practice in Region VII and we assume in other hog growing regions to use Emtrymix, a turkey medication, to treat swine. The practice has gone on for years. When instances come to our attention, we notify responsible parties via NAF, but this seems to be an industry-wide problem. We know of no health or residue problems associated with this misuse, but this does represent what we believe to be extensive extra-label use of a drug.

5. DOC 84-353-189 represents Emtrymix sold to Elbing Grain Co., Elbing, KS. of the firm, states they sell the drug to local farmers for use in swine. They neither hold an FD-1800 nor have they provided a statement to Pro Ag they will sell only to FD-1800 holders.

6. DOC 84-352-730 represents Emtrymix sold to Linn County Vet Clinic, Centerville, KS. stated he prescribes the drug for bloody scours in swine. He stated he does not hold an FD-1800 and neither do the farmers to whom he prescribes the drug.

A draft Regulatory Letter outlining 501(a)(5) and 502(f)(1) violations is attached. The consignees in 1, 4, 5, and 6 above also caused 501(a)(5) adulteration of a drug. We will notify them via NAF.

James E McDonald
/s/ James E. McDonald
Compliance Officer

Mary Woleske
/s/ Mary Woleske
Director, Compliance Branch

Attachments: Draft Regulatory Letter
Via DHL: Cy C/R's, rcrds & lblg - subj spls
Cy EIR 6/6-8/84

cc: HFA-224; SJ; EIR; W/RP; RF; IBRF

JEM:rs

Via DEC

Mr. **Weiss**. Why would FDA not have discovered this widespread misuse before and done something about it?

Dr. **Crawford**. Well, as I said, we became—we began receiving reports on it in 1982 and by 1984 Kansas City had confirmed that it was a problem. We are dealing with it basically when we got these reports and were able to confirm the misuse of the product, which we completed in 1984.

Mr. **Weiss**. But as of now, you apparently have done nothing about it.

Dr. **Crawford**. Well, except to try to get a better method so we could detect it and, also, to determine what the extent of misuse was. But in terms of have we taken steps to take it off the market, Mr. Chairman, the answer to that is no; that is right.

Mr. **Weiss**. I find that really difficult to comprehend, given your own attitude concerning the danger of this kind of misuse. In any event, you will review all that for us——

Dr. **Crawford**. I will.

Mr. **Weiss**. And come in with some information for us tomorrow. Is it permissible under CVM's current extra-label use policy for a veterinarian to use a new animal drug for an unapproved purpose if he does so within the confines of valid veterinarian/client/patient relationship?

[The policy referred to follows:]

FOOD AND DRUG ADMINISTRATION
COMPLIANCE POLICY GUIDES

GUIDE 7125.06

CHAPTER 25 - ANIMAL DRUGS

SUBJECT: Extra-Label Use of New Animal Drugs in Food-Producing Animals

BACKGROUND

Concern over the extra-label use of drugs in treating food-producing animals and the possiblity that human food may become adulterated with illegal drug residues from such misuse has prompted a revision in the Center for Veterinary Medicine (CVM) extra-label drug use policy. Under the revised policy, a finding of illegal drug residues no longer will be a prerequisite for initiating regulatory action based on extra-label drug use of drugs in food-producing animals.

For the purpose of this policy, "extra-label use" refers to the actual or intended use of a new animal drug in a food-producing animal in a manner that is not in accordance with the drug labeling. This includes, but is not limited to, use in species or for indications (disease or other conditions) not listed in the labeling, use at dosage levels higher than those stated in the labeling, and failure to observe the stated withdrawal time.

FDA in the past has not sanctioned extra-label uses of drugs in food-producing animals, but the agency has stated that it would refrain from instituting regulatory action against licensed veterinarians for using or prescribing in their practices any drugs they could legally obtain. Nevertheless, it has been FDA's position that veterinarians may be subject to regulatory action for any violative drug residues in human food resulting from their prescriptions, recommendations, or treatments contrary to label instructions. Similarly, anyone in the producing or marketing chain who could be shown to have caused illegal drug residues through extra-label use of drugs in food-producing animals has been subject to regulatory action.

POLICY

The use or intended use of new animal drugs in treating food-producing animals in any manner other than in accord with the approved labeling causes the drugs to be adulterated under the Federal Food, Drug, and Cosmetic Act (the Act, (sections 501(a)(5), 512(a)(1)(A) and (B)). The agency will consider regulatory action when such use or intended use is found, whether by a veterinarian, producer, or other person. Regulatory actions will also be considered against distributors and others who might cause adulteration of approved new animal drugs. Nevertheless, extra-label drug use in treating food producing animals may be considered by a veterinarian when the health of animals is immediately threatened and suffering or death would result from failure to treat the affected animals. In instances of this nature regulatory action would not ordinarily be considered provided all of the following criteria are met and precautions observed:

1. A careful medical diagnosis is made by an attending veterinarian within the context of a valid veterinarian-client-patient relationship[1];

2. A determination is made that, (a) there is no marketed drug specifically labeled to treat the condition diagnosed, or (b) drug therapy at the dosage recommended by the labeling has been found clinically ineffective in the animals to be treated;

3. Procedures are instituted to assure that identity of the treated animals is carefully maintained; and

4. Significantly extended time period is assigned for drug withdrawal prior to marketing meat, milk, or eggs; steps are taken to assure that the assigned timeframes are met, and no illegal residues occur.

Extra-label use of drugs in treating food-producing animals may under this policy, therefore, be considered only in special circumstances. The "exempting" criteria do not include drug use in treating food-producing animals by the layman. Lay persons cannot be expected to have sufficient knowledge and understanding concerning animal diseases, pharmacology, toxicology, drug interactions, and other scientific parameters to use drugs in treating food-producing animals in any way other than as labeled.

Certain drugs may not be used in treating food-producing animals even under the cited criteria. This includes chloramphenicol. Extra-label uses of drugs in treating food-producing animals for improving rate of weight gain, feed efficiency, or other production purposes, or for routine disease prevention are inappropriate as is use for therapeutic purposes other than under the circumstances described above. Also, the exception cited above does not sanction the sale and use, for any purpose, of new animal drugs that are not approved, such as diethylstilbestrol (DES).

REGULATORY GUIDANCE

Guidance for investigations and regulatory action recommendations will be issued separately.

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[1] A valid veterinarian-client-patient relationship, as defined by the American Veterinary Medical Association is the following:

"An appropriate veterinarian-client-patient relationship will exist when: (1) the veterinarian has assumed the responsiblity for making medical judgements regarding the health of the animal(s) and the need for medical treatment, and the client (owner or other caretaker) has agreed to follow the instructions of the veterinarian; and when (2) there is sufficient knowledge of the animal(s) by the veterinarian to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s). This means that the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of an examination of the animal(s), and/or by medically appropriate and timely visits to the premises where the animal(s) are kept; and when (3) the practicing veterinarian is readily available for follow-up in case of adverse reactions or failure of the regimen of therapy."

Issued 03/09/84
Revised 05/01/84

Dr. **Crawford**. Yes, it is, with some exceptions. There are some products that are labeled "Not for Use in Food-Producing Animals." These products may not be used under any circumstances in food-producing animals. There also is the category of feed additives. Feed additives may not be used extra-labelly. They must be used only as labeled. However, the exception which allows veterinarians, when they have a veterinarian/client/patient relationship, to use these products in their own practices, refers largely to those situations where no drug exists to treat certain disease conditions and where the drug is approved for some use in some species and, therefore, has gone through the FDA approval process. It is an attempt to allow the use of these drugs where alternatives do not exist. In many cases, as you would know, life and death matters. There are also many cases where, in the veterinarian's judgment, if the extra-label use is not employed, there will either be human disease or there will be animal disease and death. So it is allowable under those kind of controlled circumstances for the veterinarian to make that distinction; not the layman, but the veterinarian.

Mr. **Weiss**. A July 1, 1985, CVM compliance memorandum states that, "Despite our concern about dimetridazole use in swine, we have not yet made the policy decision to stop the use of this drug by veterinary practitioners."

[The memorandum referred to, and relevant supporting documents, follow:]

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

JUL - 1 1985

Memorandum

Date
"Director, Division of Compliance, HFV-230
Center for Veterinary Medicine

From
85-462-888, et al, Emtrymix
(Dimetridazole) Premix
Subject
(Re: Your submission of 5/14/85)

Kansas City District, HFR-7140
To
Attention: Gerald C. Klemm
Compliance Officer

Veterinary Clinic, P.C.
, Iowa

INJUNCTION TEMPORARY ABEYANCE
SEIZURE RECOMMENDED

We are unable to concur in your proposed injunction. We agree that violations do exist since Emtrymix is distributed to Veterinary Clinic who sells it to farmers for use in the manufacture of swine feeds. Neither the veterinary clinic nor the farmers hold approved FDA 1800s providing for the legal distribution of Emtrymix. Even if they did, the approval would be invalidated upon use of the premix in swine feeds since the premix is approved for use in turkey feeds only. Nevertheless, we believe that the principal violator in this triangle is Iowa Veterinary Supply who violates the provisions of Section 512 (a)(1) and 21 CFR 510.7. While the veterinary clinic technically violates the same sections, the premix is apparently distributed within the confines of a valid professional practice.

Representatives of the veterinary clinic claim that they are operating within the provisions of the "extra-label use policy." Investigations at the clinic and at the farms of three clients of the clinic veterinarians indicate, if not conclusively establish, that the criteria contained in Compliance Policy Guide 7125.06 are not being met. Investigations at the farms found that Emtrymix was being used at lower concentrations than the one to two pounds per ton the clinic veterinarians claim to have recommended; Emtrymix was being used in combination with other drugs in feeds (the clinic veterinarians didn't address this); and Emtrymix was being used for "maintenance" rather than for treatment of outbreaks of swine dysentery.

In spite of all the above, the Center stated in the chloramphenicol assignment of March 1, 1984, that chloramphenicol was to be the initial focus of the revised extra-label use policy, and despite our concern about dimetridazole use in swine we have not yet made the policy decision to stop the use of this drug by veterinary practitioners. Until a policy decision is made on dimetridazole, or any other drug, to pursue extra-label use violations as we did on chloramphenicol, we are not prepared to pursue Section 501 (a)(5) extra-label use violations per se by practitioners, even if it involves premixes requiring approved FDA 1800s.

We are now in the process of reviewing the safety data available for dimetridazole and ipronidazole to reevaluate the use of these drugs. In the meantime, we will consider regulatory action, including injunction, against premix distributors, such as Iowa Veterinary Supply in this case, based on the sale of FDA 1800 premixes to firms or individuals, including veterinarians, who do not hold the required approval. We believe this approach will have a much broader corrective effect, will avoid the appearance of inequitable enforcement inherent in taking action against individual practitioners in situations such as this, and is a much more clean cut action not involving the practice of veterinary medicine.

With regard to dimetridazole premix in the possession of the veterinary clinic, we would be willing to consider seizure if you can provide assurance that seizure could be accomplished at a time when a substantial quantity of premix is available at the clinic. The distinction we are making, and our reason for being willing to consider seizure but not injunction at this time, is that the premix as it sets at the clinic is adulterated as a matter of law. Section 512 deems the premix in the possession of the clinic unsafe for the purposes of section 501(a)(5) because at the time of its removal from the distributor (Iowa Veterinary Supply), the distributor did not have an unrevoked written statement from the consignee (Veterinary Clinic), or notice from the Secretary, to the effect that the consignee is either the holder of an approved FDA 1800 or that the consignee will ship the drug only to a holder of an approved FDA 1800.

This approach is more clearly supportable because it has nothing to do with the extra-label use policy. The extra-label use policy provides veterinarians with an exemption from section 512(a)(1)(B) when the criteria contained in CPG 7125.06 are met. The extra-label use policy does not address and does not provide anyone with any exemption from the requirements of the second paragraph of section 512 paraphrased above. The requirements of this paragraph apply to all premixes requiring approved FDA 1800s, including those for which we are not anticipating any class action. Incidentally, the language of section 512 seems to place the responsibility for violations on the distributor of the premix more so than on the consignee. At any rate, seizure would be against the violative article rather than against the responsible individuals regardless of who has possession of the article at the time of seizure.

If you consider seizure feasible, we suggest you submit a seizure recommendation confirming that the violation still exists and that a significant quantity of premix can be expected to be available for seizure. The charge on which the seizure would be based is a fairly straightforward 501(a)(5) charge based on the absence of an unrevoked statement to the effect that the clinic is either the holder of an approved FDA 1800 or that it will supply the premix only to holders of approved FDA 1800s. At this time we do not believe we could approve a similar seizure at Iowa Veterinary Supply because the premix does not become adulterated until it is consigned to a person who is not authorized to receive it. We also would not be willing to approve seizure at the clinic in this or similar situations even in the absence of an unrevoked statement, if it could not be shown that the premix is being sold to producers who do not hold approved FDA 1800s.

We appreciate your efforts in developing this recommendation and your District's other efforts with respect to dimetridazole use in swine. These have clearly brought to the Center's attention the widespread abuse of this toxic drug. And while a specific action like the injunction requested is a bit premature, it has materially aided in pushing along the policy decision.

Edward J Ballitch
Edward J. Ballitch

Concur: William B. Bixler
William B. Bixler, VMD
Associate Director for Surveillance and Compliance

Concur: Richard H. Teske
for Lester M. Crawford, DVM, PhD
Director, Center for Veterinary Medicine

cc: HFR-7100
HFC-102
HFC-214
HFV-1
HFV-230
HFV-236(HR/RI5-013)
HFA-224
DDean/pa 6/12/85
initialed by Mr. Ballitch:6/26/85
DDEAN:dp:6/27/85final

DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION, REGION VII

Memorandum

Veterinary Clinic
, IA 51346

Date May 14, 1985

From Kansas City District
Compliance Branch/HFR-7140

Subject 85-462-888, Entrymix (Dimetridazole), et al.

To CENTER FOR VETERINARY MEDICINE
CASE GUIDANCE BRANCH/HFV-236

RECOMMENDATION FOR INJUNCTION - NON-ROUTINE

Attached is our recommendation to enjoin the referenced firm and its four practicing veterinarians who are members of this Professional Corporation from obtaining and commercially marketing Entrymix (dimetridazole) premix and any other NAD in violation of the requirements of the Federal Food, Drug, and Cosmetic Act.

KAN-DO is submitting this recommendation as NON-ROUTINE since it presents a new issue of FDA policy. We have concluded this recommendation is non-routine since it involves the retail sale by a veterinary Clinic of 50 pound bags of a drug premix (Entrymix) which is approved only for turkeys, to clients for mixing with feed to be fed to swine herds to treat swine dysentery. Also, Entrymix requires an FD-1800 approval to mix into feed. Neither the clinic or their clients hold the required approval. We are not requesting a TRO because our investigation has not revealed any tissue residue reports involving dimetridazole or any reports of injury to swine which have consumed this drug.

In addition to the recommendation, we have prepared the following for your review.

a) Proposed letter to U.S. Attorney
b) Proposed Complaint for Injunction

Veterinary Clinic, P.C. and its owners have been previously informed by Notice of Adverse Findings Letter dated November 26, 1984 of the violative nature of the manner with which they were selling Entrymix and the most recent inspection.

During an inspection of a veterinary drug distributor (Iowa Veterinary Supply Company, Iowa Falls, Iowa) it was revealed that significant quantities of Entrmix (dimetridazole) premix was being sold to Veterinary Clinic, P.C. Iowa.

Entrymix premix is manufactured by Salsbury Laboratories, Charles City, Iowa, and is approved only for the prevention and control of Blackhead, growth promotion and feed efficiency for turkeys. The label directions say it should not be fed to turkeys for more than 7 days (0.06 - 0.08%) and instructs the user to withdraw the drug 5 days prior to slaughter (0.015 - 0.08%).

RD 5.013
5-20-85

The initial inspection of this firm on 11/2/84 confirmed their receipt and sale of Entrymix to swine producers with instructions to mix 1-2 pounds Entrymix/ton feed to treat bloody scours in swine with a recommended 30 day withdrawal time prior to slaughter. The firm purchased 3,100 pounds (62/50 pound bags) of Entrymix between January 1, 1984 and September 21, 1984. During the inspection the investigator was furnished copies of invoices which only account for 2,200 pounds (44/50 pound bags). Although the clinic owns a mixer, they do not compound this prescription. Instead, they sell intact 50 pound bags to the swine producer and provide instructions on how to mix the drug. Copies of client sales receipts (invoices) obtained during the 11/2/84 and 3/20/85 EI's at the firm verify the OTC sales of Entrymix premix since they bear no mileage charge or notations reflecting animal treatment by the veterinarians. Also, the sales receipts copies furnished to FDA by Dr. Kreykes, indicate the sale of "D-Med" or "entryl" instead of Entrymix premix. KAN-DO has no information explaining the reason for this method of invoicing Entrymix.

Dr. Edwin J. Kreykes, DVM defended the clinics sales of Entrymix for swine dysentery for being within the practice of veterinary medicine and in line with FDA's policy on extra-label use of drug products. Dr. Kreykes told the investigator it is common knowledge that Entrymix is effective against swine dysentery and produced a copy of a pamphlet published by Swine Dysentery Committee, Livestock Conservation Institute, South St. Paul, MN, to support his statement. The pamphlet, copy attached to EIR dated 11/2/84 as Attachment 2, recommends mixing dimetridazole in drinking water to treat swine dysentery and recommends an extended 30 day withdrawal time. Page 10 of the pamphlet bears a statement which acknowledges Pfizer, Inc., and Salsbury Laboratories, Inc., for their financial support for the first printing.

A Notice of Adverse Findings letter issued to the firm on 11/26/84 advising that the Entrymix they were receiving from Iowa Veterinary Supply Company was being obtained illegally and was not being distributed in accordance with the requirements of Section 512. The letter also advised them firm that the extra label use policy does not apply to illegal drugs. A copy of Section 512(a)(1) of the Act accompanied the letter.

The firm and the four partners responded to our NAF letter on 12/24/84 stating they will curtail the use of Entrymix in the future and requested clarification of why their firm is considered to be any different from the supplier who sells them Entrymix since they are not the final users of the drug. KAN-DO responded to the inquiry on 1/3/85 referring them again to Section 512(a)(1) of the Act and telling them our inspection showed their clinic did not hold approval to obtain Entrymix and was selling it to consignees who did not hold approval to mix this drug with animal feed.

Since Veterinary Clinic, P.C. advised KAN-DO by letter dated 12/24/84 they would curtail the use of Entrymix, another inspection of the clinic was conducted on 3/20/85 to confirm their statements. Review of firm files revealed the firm received 800 pounds Entrymix since the first of the year

(1985) and sold all except one 50 pound bag. This bag was officially sampled and assigned sample number 85-462-888. Through the employees search of records only 456 pounds of Entrymix could be accounted for. Review of the account cards for the clients who purchased Entrymix showed periodic visits to the consignees. A printout was obtained at Iowa Veterinary Supply Company which shows all sales of Entrymix to Veterinary Clinic since 11/3/84. The printout shows Veterinary Clinic has purchased 2,400 pounds Entrymix premix since 11/3/84, and 1,100 pounds of this total since 1/2/85. Since the record review only accounted for 456 pounds, and the customer account cards showed periodic visits to the consignees, KAN-DO can only speculate how the remaining 644 pounds was distributed.

During the 3/20/85 inspection Edwin J. Kreykes, DMV told the investigator that nothing has changed since the previous inspection (11/20/84) regarding his firm's use of Entrymix. He stated that his firm still does not hold approval to receive the drug and, to the best of his knowledge, his clients do not hold approved FD 1800's for Entrymix. Dr. Kreykes said it did not make any difference because it was used to treat swine dysentery in hogs and not for its approved use in turkeys.

Dr. Kreykes told the investigator his firm recommends the use of 1-2 pounds Entrymix/ton of feed and an extended withdrawal time of thirty days. Dr. Kreykes said Entrymix is only prescribed if other medications had failed and the animals life was immediately "threatened."

Dr. Kreykes provided the investigator with copies of an article from FDA Veterinarian, March, 1984 "Questions and Answers and FDA's Policy on extra-label use of animal drugs" and the previously referred to pamphlet on Swine Dysentery published by the Swine Dysentery. (Copies attached to EIR 3/20/85) It is interesting to note the pamphlet no longer acknowledges the financial support by Pfizer, Inc. and Salsbury Laboratories, Inc. as in the first printing.

The investigator warned Dr. Kreykes of his responsibilities under the Act and of possible penalties for violation of the Act. Dr. Kreykes maintained the position that his firm was using Entrymix legitimately within the practice of veterinary medicine.

Distribution information obtained from Iowa Veterinary Supply Company, Iowa Falls, Iowa, shows that Veterinary Clinic purchased 500 pounds Entrymix on March 28, 1985. This purchase was about a week after an FDA inspection during which Dr. Kreykes was warned of his responsibilities under the Act.

On 4/2/85 an FDA investigator visited three clients selected at random, who were listed in Veterinary Clinic records having received Entrymix. Sample numbers DOC 85-462-681/2/3 represent documents associated with these visits. A more detailed accounting of the facts obtained during these visits appears within the body of the Recommendation for Injunction. In summary, the three consignees each raise from 500 - 1,000 hogs/year. Each feed Entrymix-containing feed to their herds to treat bloody scours. Each obtain the Entrymix from Veterinary Clinic and use 1/2-1 pound Entrymix/ton of feed, mixed in their own mixers. They each said the veterinarians recommended a 7-14 day withdrawal time. In addition, each of these hog farmers has purchased Entrymix from Veterinary Clinic since 1-3-85 (date of KAN-DO's response to Veterinary Clinic letter dated 12-24-84).

Based on the inspectional evidence at hand it is apparent that Veterinary Clinic, P.C., and Drs. Weber, Schultz, Christenson and Kreykes have no intention of voluntarily bringing their firm in compliance with the requirements of Section 512(a)(1) and 512(a)(2) of the Act with regards to the purchase and sale of Entrymix premix. Therefore, KAN-DO recommends this firm and individuals be enjoined from this practice.

Our review of the facts reveals the following violations of the Act:

1. Section 501(a)(5) - Veterinary Clinic, P.C. is causing Entrymix (dimetridazole) premix to be a new animal drug which is unsafe within the meaning of Section 512 because they are purchasing significant quantities and promoting it for treatment of swine dysentery at levels of 1-2 pounds of premix/ton feed and recommending a 30 day withdrawal time. This drug has been determined to be effective for the treatment and control of Blackhead in turkeys when given at 0.015%-0.08%. When fed to turkeys at levels of 0.06-0.08% it should be discontinued after seven days. When fed to turkeys at any of the approved levels the turkeys should be withdrawn from the medicated feed ration for at least five days prior to slaughter. Scientific data supporting the safe use and effectiveness of Entrymix (dimetridazole) in turkeys appears in NADA 014-613 assigned to Salsbury Laboratories, Charles City, IA. There is no approved NADA to support the prescribed dosage level or withdrawal time, safety and effectiveness of dimetridazole in swine.

2. Section 512(a)(1) and 512(a)(2) - Veterinary Clinic, P.C. is regularly obtaining significant quantities of Entrymix (dimetridazole) premix from Iowa Veterinary Supply Company, Iowa Falls, Iowa, in the absence of an unrevoked written statement to the effect that, with respect to the use of such drug in animal feed:

(i) Veterinary Clinic is the holder of an approved application under subsection (m) of Section 512;

(ii) will, if Veterinary Clinic is not a user of the drug, ship such drug only to a holder of an approved application under subsection (m) of this section.

This firm is continuing sales of Entrymix (dimetridazole) premix to clients who they know do not hold approved FD-1800's which would legally permit the manufacture of feed using this drug. KAN-DO was able to obtain a copy of a letter dated 12/29/83 issued from Veterinary Clinic and signed by Keith Weber, a DVM and one of the firms partners. The letter is addressed to

Iowa Veterinary Supply, Sioux City, Iowa. (The Sioux City location is an extension of the Iowa Falls, Iowa firm). The letter appears to be an "unrevoked statement of intent" as provided for under Section 512 of the Act. It states in part, "All 1800 Feed Grade Antibiotics are to be sold only to persons with 1800's." Since this letter refers to only to Feed Grade Antibiotics it does not encompass the purchase, receipt and subsequent distribution of Entrymix (dimetridazole) premix. The existence of this letter appears to indicate that Dr. Weber and Veterinary Clinic were knowledgeable of the requirements of Section 512 at least 11 months prior to receiving the Notice of Adverse Findings letter in late November, 1984. A copy of the 12-29-83 letter is enclosed.

Although Iowa Veterinary Supply Company, Iowa Falls, Iowa, is attempting to obtain a "Letter of Intent" from Veterinary Clinic which applies to Entrymix, KAN-DO plans to issue a Notice of Adverse Findings letter to Iowa Veterinary Supply company regarding their responsibility under Section 512 of the Act.

3. Section 501(a)(6) - Veterinary Clinic, P.C. is causing Entrymix (dimetridazole) premix, a new animal drug which is only approved for treatment of prevention of Blackhead in turkeys under strict controls, to be incorporated in a medicated feed ration and fed to swine under controls which have not been scientifically tested and evaluated by experts and determined to be safe, therefore is unsafe within the meaning of Section 512.

Veterinary Clinic, P.C. (Dr. Edwin J. Kreykes, DVM) maintains their firm's practice of selling Entrymix to treat swine dysentery is within the legal practice of veterinary medicine and meets FDA's extra-label use policy for animal drugs. KAN-DO disagrees. The inspectional facts clearly show that three of the clinic's consignee's visited at random are not mixing Entrymix feed at the potency level recommended by Dr. Kreykes. Also, two of the consignees admit they are mixing other drugs with the Entrymix feed, namely Aureomycin and ASP-250, without the knowledge of anyone associated with Veterinary Clinic, P.C. Examination of Veterinary Clinic, P.C. sales invoices revealing continued sales of Entrymix premix to the same consignee over a period of more than 14 months does not support a "one time use" theory regarding all approved drugs being tried and found to be ineffective.

Dr. Kreykes told FDA investigators' on 11/2/84 and 3/20/85 that he and his associates are recommending an extended 30 day withdrawal time for Entrymix. The three clients who were selected at random each stated they were told by the veterinarians to withdraw Entrymix from swine 7-10 days prior to slaughter. Two of the clients who were selected admitted to the investigator they prefer to keep visitors to their farm to a minimum to reduce the chances of introducing human borne viruses or bacteria to their herds. One of the clients admitted he considered using Lincomix for bloody scours treatment but the cost factor causes him to use Entrymix. Reportedly it takes 5 pounds Lincomix/ton to achieve the same results as 1/2 pound Entrymix/ton.

During the inspections of 11/2/84 and 3/2/85 at Veterinary Clinic, P.C. and the inspections on 4/2/85 at three clients chosen at random, neither Dr. Kreykes nor any of his clients mention or refer to any procedure which may have been instituted to assure that identity of the treated animals was carefully maintained.

These are the reasons we believe that a valid doctor/client/patient relationship has not been demonstrated by interviews with three clients who purchase Entrymix premix from Veterinary Clinic, P.C. Had a valid doctor/client/patient relationship existed there would not be so many descrepencies and widespread use of Entrymix premix in treating swine dysentery.

As previously stated, Entrymix (dimetridazole) premix is manufactured by Salsbury Laboratories, Charles City, IA, under approved NADA 014-613. KAN-DO has attached a copy of an affidavit dated 2/27/85 by Robert R. Baron, Director of Regulatory Affairs, Salsbury Laboratories which states that all dimetridazole used in the production of Entrymix premix originates from Rhone-Poulenc, Inc., located in France. Mr. Baron refused to sign the affidavit per corporate policy but agreed the contents was accurate. KAN-DO feels this affidavit adequately supports the I.S. requirement of the prohibited acts chapter of the Act.

We propose injunction as the recommended action of choice in this case to curb the widespread, continued misuse of dimetridazole in treating swine dysentery. Veterinary Clinic, P.C. is a partnership of four duly licensed veterinarians which is located within the heart of Iowa hog country. The attached EIR's and affidavits dated 11/2/84 and 3/20/85 and the subject samples provide the necessary evidence to support this action. Your prompt review is requested. You may refer any questions regarding this submission to Gerald C. Klemm at FTS 8-758-5521.

Gerald C. Klemm
/s/ Gerald C. Klemm
Compliance Officer

G E Vince
/s/ Gerald E. Vince - Approve
Director, Compliance Branch

James A. Adamson
/s/ James A. Adamson - Concur
District Director

Clifford S. Shane
/s/ Clifford S. Shane - Concur
Regional Food and Drug Director

Enclosures: Injunction Recommendation
Draft Ltr USA
Draft Complaint for Injunction
cy EIR 11/2/84; cy NAF 11/26/84
cy Response to NAF 12-24-84
cy Response to firm 1-3-85
cy EIR 3-20-85; cy 12/29/83 ltr from HVC to IVS
cy C/R's and affidavits

cc: HFA-224; Inj Jkt; EIR; SC/RP; DM/RP; RF; IBRF

GCK:bl

VIA DEC

Mr. Weiss. Does this mean that veterinarian use of dimetridazole to treat dysentery in swine may be permissible under CVM's extra-label use policy?

Dr. Crawford. No. There are drugs that are labeled specifically to treat what is called swine dysentery, including one that was approved in 1983. So the extra-label use policy does not, strictly speaking, apply to the use of this drug. It would apply in those cases where no drug exists to treat——

Mr. Weiss. This is not one of those situations?

Dr. Crawford. No.

Mr. Weiss. I think this may be a good time for us to take a break. The bells have sounded for a vote on the floor. So we will take a recess for about 15 minutes.

[Recess taken.]

Mr. Weiss. The subcommittee will come to order.

Dr. Crawford, doesn't section 512(a)(1) of the Food, Drug, and Cosmetic Act flatly prohibit any unapproved use, including that by a veterinarian, of a new animal drug?

Dr. Crawford. Let me confer with my colleague on that, please.

[Pause.]

Dr. Crawford. Yes. It is believed by FDA, Mr. Chairman, that in—that veterinarians, at least, can have the latitude to use these drugs for so-called extra-label purposes when this is necessary for the benefit of man and animal. And it is not believed by us that that particular section of the Act prohibits these uses.

Mr. Weiss. Dr. Guest, in an interview in the March 9, 1984, FDA Veterinarian, explaining the agency's current extra-label use policy, you acknowledged: "The use of drugs in treating food animals in any way other than in accord with approved labelling is technically a violation of the law. This has been true for many, many years."

[The interview referred to follows:]

AN INTERVIEW WITH
DR. GERALD GUEST

Questions & Answers on FDA's Policy on Extra-Label Use of Animal Drugs

The **FDA Veterinarian** has received a number of inquiries over the past few weeks concerning the Bureau of Veterinary Medicine's revised policy on extra-label use of drugs. As a service to our readers and an effort to help clarify the policy, we have asked Dr. Gerald B. Guest, deputy director of FDA's Bureau of Veterinary Medicine, to respond to some of these questions.

Q. You are obviously aware that BVM's extra-label veterinary drug use policy has created not only great interest and concern but even some confusion in the veterinary profession as well as among veterinary drug distributors. Can you clear the air on this and explain what the policy really means in practical terms?

A. Certainly I can explain the policy, and hopefully I can clear the air at the same time. In the most elemental terms, the policy says that the use of drugs in treating food animals in any way other than in accord with approved labeling is technically a violation of the law.* This has been true for many, many years.

Q. What, then, has actually changed if the law is intact?

A. What has changed is FDA's enforcement policy. In the past we took the position that a practicing veterinarian could use any drug in treating animals in any manner he or she chose, within good professional ethics, provided that no illegal residues were found to be present in treated food-producing animals. Since extra-label drug use is a violation of the law, our current policy specifically affirms the fact that FDA may take regulatory action even if no illegal residues are shown to be present. This is a fundamental change in our regulatory philosophy.

Q. Why was BVM's regulatory philosophy changed?

A. The answer is simply and basically to protect the public health. Extra-label use of drugs in treating animals has become routine practice in some areas. It is discussed in some veterinary texts; it is discussed in most veterinary medical schools; it is widely practiced by the veterinary profession.

Our greatest concern regarding the extra-label drug use practice is the potential impact it has on the safety of the nation's meat, milk, and egg supply. Extra-label use of drugs can result in residues in edible products of treated animals. And these residues can escape detection because often there are no adequate analytical methods for the USDA's Food Safety and Inspection Service to utilize in its national residue monitoring program. As public health officials, this naturally concerns us. And it should also be a natural concern to the veterinary profession and the agribusiness community who provide animal protein foods to the American public, and who may be placing their markets in jeopardy.

Dr. Gerald B. Guest

Our hope in the Bureau of Veterinary Medicine is that—through all of the recent dialogue that has been initiated, through all of the ideas and opinions that have been exchanged, and through all of the activities that have taken place surrounding this issue—we have been able to cause a renewed awareness of the gravity of the decision to use an animal drug outside of label directions. A decision that should be most carefully considered and most judiciously applied.

Q. You mentioned food-producing animals. Does this policy apply also to the treatment of pets and other non-food animals?

A. No, it does not. The focus of the policy is upon drug use in food-producing animals because of the direct public health implications. While extra-label drug use is illegal under the law for all animal treatment, we would not take a regulatory posture in the case of extra-label use by veterinarians in treating non-food animals unless, of course, it is evident in a particular case that the public health or the health and welfare of the animal were in jeopardy, or if other serious consequences occurred.

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*The "law" refers to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 351 (a)(5), 352(f)(2), 360b(a)(1)(A)(B).

Q. Are there any exceptions to this prohibitive policy?

A. We recognize, of course, that there will be instances where there is simply no drug on the market that is labeled to treat the diagnosed condition. In these cases we would not ordinarily consider regulatory action—provided, of course, that certain criteria are met and certain precautions are observed. We all recognize that while the veterinary profession has a substantial armamentarium of drugs available, there are voids that may occur occasionally. Fortunately, however, these voids are rare.

Q. Can you describe the conditions under which extra-label drug use in food animals would be acceptable?

A. First of all, the policy does not apply to the layman. Only a licensed veterinarian can be expected to have sufficient knowledge about animal diseases, pharmacology, toxicology, drug interactions and other scientific factors to use drugs in any way other than as labeled. Second, the policy presupposes the existence of a *valid* veterinarian-client-patient relationship.

The American Veterinary Medical Association [AVMA] has recently adopted a definition of a legitimate veterinarian-client-patient relationship which includes three basic elements: one is responsible veterinary judgements, two is first-hand knowledge of the animal's condition, and three is adequate follow-up to assure the success of the treatment. [*Journal of the American Veterinary Medical Association, February 1, 1984, page 241.*]

So, to answer your question, given the AVMA definition, our policy is that regulatory action by FDA would generally not be considered if the veterinarian makes a reliable medical diagnosis; if there are no marketed drugs specifically labeled for the conditions diagnosed, or if the labeled dosage is inadequate for the condition; if identity of the treated animal is maintained; and, if significantly extended time periods are followed before meat, milk, or eggs are marketed for food.

We must keep in mind, however, that no matter how scrupulously these criteria are met, the bottom line of the policy—and the law—remains unequivocally that no illegal drug residues can be found to occur in any food-producing animal that has been treated by extra-label use of a drug.

AVMA Criteria For A Valid Veterinarian-Client-Patient Relationship

1. The veterinarian has assumed the responsibility for making medical judgements regarding the health of the animal(s) and the client (owner or other caretaker) has agreed to follow the instructions of the veterinarian.
2. There is sufficient knowledge of the animal(s) by the veterinarian to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s). This means that the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of an examination of the animal(s), and/or by medically appropriate and timely visits to the premises where the animal(s) is kept.
3. The practicing veterinarian is readily available for follow-up in case of adverse reactions or failure of the regimen of therapy.

Q. Under this policy, then, extra-label use of drugs in food-producing animals may be considered by a practicing veterinarian only in certain circumstances. Is that correct?

A. That is correct.

Q. But, as long as these criteria are met and a valid veterinarian-client-patient relationship exists, you're saying that any drug can be used. Is that correct?

A. No, I'm not saying that. Clearly, diethylstilbestrol—DES—may not be used under any circumstances. DES was withdrawn from approval in 1979 and there is no conceivable use in food animals which warrants the exposure of consumers to residues of DES. Similarly, chloramphenicol may not be used in food-producing animals because the risk of residues associated with its use will virtually always offset any perceived benefits over other available drugs. Chloramphenicol is approved for use only in treating dogs, and the labels are required to bear a warning against use in food-producing animals [21 CFR 555.110, et seq.]. Standard medical and toxicology texts warn that the risks associated with this drug are *not* related to dose.

Q. Are there any other drugs that fall into this category?

A. Extra-label use of drugs for growth promotion or other production purposes—or for routine disease prevention—is inappropriate because the expected economic benefit does not outweigh the public health risk. Extra-label use of any drug should be considered *only* when the health of treated animals is immediately threatened, and if suffering or death would result from a failure to treat affected animals.

Q. What is the reaction of veterinarians to this policy?

A. Generally, I have found it to be quite positive. Reassuringly positive. Most practitioners who have contacted me personally about the policy recognize that a problem exists and that control of drug usage needs to be strengthened. Of course, there are those who disagree. But maybe they don't fully understand our policy and its basis. Maybe this discussion will help. Significantly, however, the AVMA is on record as supporting our position, and they are helping to get the word out to their constituency.

Specifically, the AVMA has expressed its support in a letter to Dr. Crawford on January 6, 1984. Here is what that letter stated:

> *AVMA acknowledges the role of the veterinary medical profession and livestock agriculture in the protection of public health through the responsible use of animal drugs. Further, the AVMA favors FDA's taking corrective action when the flagrant misuse of a drug product has the potential for causing harmful drug residues in food for man. To those ends, the Association intends to cooperate with FDA in its efforts to reinforce proper drug usage, minimize the occurrence of drug residues, and disseminate the latest information on the pharmacology of selected over-the-counter and prescription veterinary drugs.*

We have solid support on this issue, and that's why I am very encouraged.

Q. You mentioned that one of the criteria for extra-label use by veterinarians is an extended withdrawal time. How long should that time be? How would the attending veterinarian know what time frame to recommend?

A. That's a question I'm afraid I'm not able to answer definitively. It's also a principal reason for our concern about extra-label use. Certainly the level of concern is directly related to the proximity of treatment to the marketing of meat, milk, or eggs. Obviously, we are very concerned about the extra-label treatment of animals ready for slaughter and we are less concerned about the treatment of breeding stock or replacement animals which are not intended for slaughter or food production within a short time frame. A veterinarian can draw upon practice experience, knowledge of drug pharmacology, references to medical texts and research papers, and other scientific sources in assigning drug withdrawal periods when extra-label uses are justified—according to the criteria I've already mentioned. In the absence of definitive information, however, prudence dictates that withdrawal periods for extra-label uses of drugs should be several times as long as those associated with labeled uses. The veterinarian and the producer jointly bear the responsibility for assuring that drug residue-free animals are marketed.

Q. How do you see the AVMA's definition of a valid veterinarian-client-patient relationship working in actual practice? For example, let's say that there are veterinary consultants who are not personally familiar with the animals or the premises. Yet, under these circumstances they prescribe drugs which are delivered directly from distributors to feedlots or other places where livestock is raised so that a drug supply is always on hand for use by the livestockman. Does this, in your opinion, constitute a valid relationship? Would it be acceptable?

A. No, I would think not. Not under these circumstances. An animal producer can obtain prescription legend drugs only upon a valid order of a licensed veterinarian. In addition, use of these drugs should be prescribed by the veterinarian for each specific situation following a diagnosis of the condition to be treated. The veterinarian must diagnose those particular animal conditions, or must have been on the premises recently enough to know precisely the conditions which exist so that he or she is assured that the diagnosis is correct, that the treatment is appropriate, and that the animal producer can and will use the drug correctly. This will all vary somewhat depending upon the type of production unit involved and other local factors, but certainly a casual or distant relationship does not qualify as an example of a "valid" relationship.

FDA/BVM Criteria For Extra-label Use Of *Drugs* Which Would Not Ordinarily Cause Regulatory Action By FDA

1. A medical diagnosis is made by an attending veterinarian.
2. A determination is made that (a) there are no marketed drugs specifically labeled for the conditions diagnosed, or (b) drug therapy at the dosage recommended by labeling has been found clinically ineffective in the animals to be treated.
3. The identity of the treated animals is carefully maintained.
4. Significantly extended time periods are assigned for drug withdrawal prior to the marketing of meat, milk, or eggs for food.

Even with the following of these criteria, however, FDA will consider regulatory action nonetheless if illegal drug residues are found in treated animals.

Q. Do you see drug manufacturers and distributors having any responsibilities under this policy? If so, what are they?

A. Of course, they have responsibilities. There is absolutely no question in my mind that the entire drug distribution-health care system must function responsibly. There is no question in my mind, for example, that a drug distributor is well aware of the use that will be made of shipments of chloramphenicol to feedlots. Distributors control their promotional operations as well as the activities of their sales representatives. And since they do exercise this control as part of their standard business operating procedures, it naturally follows that they may be found as contributing to or causing violations of the law under this extra-label drug use policy.

Q. If a veterinarian determines that extra-label drug use is essential in a particular situation, is it necessary to keep any special records?

A. I believe that both the veterinarian and the producer should, as a matter of good business practice, establish and maintain complete records on the situation in order to assure adequate control at the time of use and for future reference.

Q. Do you see FDA inspecting veterinary practices under this policy?

A. Let me state clearly that FDA has no intention of inspecting veterinary practices on either a routine or a random basis. Under the BVM policy, our field investigators will visit a veterinarian only when there is some specific reason to do so.

Q. What do you mean by "specific reason"?

A. I mean, for example, reasons such as the need for follow-up to reports of illegal tissue residues; the need to obtain detailed information from veterinarians attending or consulting on incidents of livestock illnesses or deaths; and the need to follow up on reports of prescription drug sales *outside* a valid veterinarian-client-patient relationship. What I am saying is that visits to veterinary practices relating to this policy will be conducted only for cause. We will not be conducting "witch hunts."

Q. Is there one final thought or statement you would like to leave with our readers on this issue?

A. Yes, there is one. This has been a particularly complex and emotionally charged issue for all concerned. With so many divergent points of view and a focal point that oftentimes appeared distant and distorted, it has sometimes been difficult for one person to understand the reason for another person's position.

But the most clarifying and refreshing aspect of all we've gone through, in my opinion, has been the reasoned discussion that has occurred between the veterinary medical profession and the Bureau of Veterinary Medicine and, most importantly, the very positive and long-term results of that discussion.

Clearly, we are all committed to pursuing the same outcome—a safe, wholesome food supply along with the ability to continue practicing good medicine. And to this end, the American Veterinary Medical Association and affiliate organizations at all levels are to be commended for their vital, dynamic role in bringing about a better understanding and a positive resolution of the issue.

All of us in the Bureau of Veterinary Medicine are genuinely gratified with the outcome; and we've learned a great deal in the process. I extend our thanks to everyone who helped in that process.

Other Items

—FDA has amended its regulations to reflect the *change of sponsor* for *iron dextran complex injection* from Fisons, Corp. to Fisons, PLC. For further information, see FEDERAL REGISTER of December 15, 1983.

—FDA has amended its regulations to reflect the *change of sponsor* for several new animal drug applications (NADAs) from Good-Life, Inc. to Central Soya Co., Inc. The NADAs include the following medicated premixes: *tylosin*, *tylosin/sulfa-methazine*, and *pyrantel tartrate*. For further information, see the FEDERAL REGISTER of December 21, 1983.

Withdrawal of Approval

—*Cooper 40% Super-T for Pigs Medicated* (tylosin phosphate), Central Soya, Co., Inc.: For making complete swine feeds used for increased rate of weight gain and improved feed efficiency. The firm requested the withdrawal of approval because the product is no longer being marketed. For further information, see the FEDERAL REGISTER of January 3, 1984.

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Mr. **Weiss**. Do you recall making that statement?

Dr. **Guest**. Yes. I wrote that as a strict reading of the law; yes, sir.

Mr. **Weiss**. What is the legal authority, then, Dr. Crawford, for CVM's policy of effectively exempting veterinarians in certain circumstances from the statutory prohibition on using new animal drugs for unapproved purposes?

Perhaps counsel, since we are asking a legal question, ought to come to the witness table and directly respond because, Dr. Crawford, I gather you are not an attorney and that you are relying——

Dr. **Crawford**. No, I'm not.

Mr. **Weiss** [continuing]. Solely on counsel's advice at this point. Is that correct?

Dr. **Crawford**. Actually, I am conferring with him on how is the best response to make, which is kind of the same thing, Mr. Chairman.

Mr. **Weiss**. Would counsel please identify himself?

STATEMENT OF MEL DROZEN, ATTORNEY, FOOD AND DRUG ADMINISTRATION

Mr. **Drozen**. Yes, Mr. Chairman. My name is Mel Drozen, and I am attorney with the Food and Drug Administration.

Mr. **Weiss**. Mr. Rosen?

Mr. **Drozen**. Mr. Drozen, D-r-o-z-e-n.

Mr. **Weiss**. Drozen. Mr. Drozen, will you raise your right hand? Do you affirm that the testimony you are about to give is the truth, the whole truth, and nothing but the truth?

Mr. **Drozen**. I do.

Mr. **Weiss**. What is the legal authority for CVM's policy of effectively exempting veterinarians in certain circumstances from the statutory prohibition on extra-label use?

Mr. **Drozen**. Mr. Chairman, I don't believe—again, I cannot speak for the agency at this point. The statutory authority—the approval requirements of the act, as you know, are found in section 512. There is a question as to whether—a legal question as to whether a new animal drug that is being used by a veterinarian, not in conjunction with an approved use, but not being—but still properly labeled, would be an approved new animal drug. Then it would become a question of whether that veterinarian is misbranding the drug by using it in an extra-label manner.

The FDA has been for a number of years trying to come to grips with the problem both in veterinary medicine, I believe, and in human medicine as to FDA's appropriate position from a legal standpoint in the interference, if you will, in the practice of veterinary medicine and human medicine insofar as extra-label use of human drugs are concerned. So there is a question as to whether, statutorily, if a veterinarian prescribes and/or administers a drug for an extra-label use, that drug would still have to require FDA preclearance under section 512; and may be misbranded under section 502 of the act. And we may be able to take legal action against it because it does not—you cannot write adequate directions for use for it for this unapproved use. But then we do get involved in the issue of whether FDA is, from a legal standpoint, unlawfully interfering in the practice of veterinary medicine, when we're talking about veterinary drugs.

I don't have the cases in front of me to cite to the Chairman, but there is a problem or an issue in regard to that.

Mr. **Weiss**. Are you familiar with *Cutler* v. *Kennedy*? In that 1979 human drug case, Judge Sirica held that, while FDA has the authority in individual cases not to take regulatory action against drugs, it had no authority to "effectively exempt" a class of drugs "from the * * * premarket licensing scheme of the Food, Drug, and Cosmetic Act."

Mr. **Drozen**. Well, Your Honor—excuse me.

Mr. **Weiss**. That's all right. No objection taken to that.

Mr. **Drozen**. A Freudian slip perhaps, Mr. Chairman.

I am familiar with the *Cutler* v. *Hayes* case and then, of course, is—we have not affirmatively in writing, I believe, or by regulation or as a matter of policy exempted a class of drugs from regulation. A recent case in the U.S. Supreme Court of *Heckler* v. *Chaney* has specifically held that the agency may exercise appropriate enforcement action in taking action against products that are illegal under the act. That specific case was FDA's not having, subject to premarket approval, specific human prescription drugs for execution purposes in various States. So we have not——

Mr. **Weiss**. That's the reason——

Mr. **Drozen**. I don't believe that what FDA is doing here is in any way an—inconsistent with the *Cutler* case and Judge Sirica's opinion. And to some extent, it is consistent with the recent decision by the U.S. Supreme Court in *Heckler* v. *Chaney*.

Mr. **Weiss**. But the *Chaney* case is the obverse of it. What it says is that FDA is not precluded from doing certain things, right?

Mr. **Drozen**. No. It says that FDA is, in effect, not obligated to take enforcement action or to require in that case premarket clearance for human drugs that were previously approved for other purposes but were being used to—or intended to be used—to execute prisoners in a number of States.

Mr. **Weiss**. Now we are talking about specific regulatory action. Section 512(a)(1) specifically prohibits any unapproved use; it states that any unapproved use is illegal. Yet FDA has now adopted a policy that authorizes such extra-label use. It just seems to me that such a policy requires statutory authorization, especially given the original scientific basis supporting the prohibition on extra-label use. Because different species have different metabolic systems, use of a drug in turkeys could have different consequences from its use in swine. I, therefore, question the statutory authority supporting your extra-label use policy. And I do not think you have really given me anything up to this point which identifies that authority. If you would like to submit a brief memorandum to the record outlining your legal position, I would appreciate it.

[The memorandum requested follows:]

The documents obtained by the Subcommittee, including the AVMA letter of 1/6/84 and public information release of 1/13/84, clearly show the important contribution by the AVMA and the Center's independent assessment and final decision.

The AVMA and others pointed out that as first announced on 8/1/83 our revised extra-label veterinary drug use policy was a terse strict reading of the Act and frankly seemed to say to veterinary practitioners, "We are going to tell you how to practice veterinary medicine." Obviously we did not intend that and believe the Subcommittee will agree that falls within the purview of state licensing authorities. As you know, the Federal Food, Drug, and Cosmetic Act does not intend to regulate the healing arts - not physicians, not dentists, not veterinarians - and the legislative history confirms this. So we were treading a fine line, but obviously for the policy to be reasonably workable some latitude was needed but with specified restrictions. The decision to recommend or not recommend legal action is committed to the Agency's prosecutional discretion. Heckler v. Chaney, 105 S. Ct. 1649 (1985). The policy sets forth guidance for use of prosecutional discretion on extra-label use of veterinary drugs.

One of the key restrictions was that the practitioners have a hands on relationship with their clients and animal patients. But we urgently needed a definition of what constituted a valid relationship which was universally applicable. That was the specific issue for which we requested the AVMA's assistance. They had the technical ability to know under various state laws what constitutes a valid practice under highly variable practice situations. A pet practice in New York City is far different than a feedlot or cow/calf practice out West. We did not accept the AVMA's proposal as initially offered but recommended changes which the AVMA announced in their January 13 release.

We believe the policy is within prudent application of the Act. While the AVMA contributed by helping with the development of the definition of a veterinarian-client-patient relationship, they did not dictate any part of the policy to the Center.

Mr. **Drozen**. The one thing I would clarify, Mr. Chairman, is that it seems to me that FDA's extra-label use policy, as I understand it, and I am not sure that General Counsel's Office was involved in drafting it, but we probably were; insofar as it relates to the extra-label use of prescription veterinary drugs, it specifically says that such use will be considered illegal by FDA, except under certain limited circumstances, as I recall. I do not have the extra-label use policy document in front of me, but my best recollection of it is that we consider extra-label use to be illegal.

Now, there are potentially different reasons for why we could, as a matter of law, consider it to be illegal, but the fact is that we do, except in the—in the situation where——

Mr. **Weiss**. Except that you are writing those exceptions into the law. There is nothing that I can see in the statute which authorizes you to make those exceptions. That is really where we disagree, and if you have any authority for making those exceptions, I wish that you would submit an explanation of it to us for the record.

Mr. **Drozen**. All right.

[FDA's explanation follows:]

The legal authority for FDA's permitting extra-label use to be considered by a veterinarian, in the context of a valid veterinarian--client--patient relationship, in very limited circumstances, is similar to the Agency's legal authority for not taking action against certain medicated blocks, sulfa drugs, and gentian violet in poultry feed. Thus, the response here is equally applicable to the Subcommittee's requests for legal authority found in questions 17, 18, and 30 submitted to the Agency by letter dated September 30, 1985.

In all of these situations, the Agency has made a decision, in effect, not to exercise its enforcement discretion. FDA's authority to exercise enforcement discretion was specifically upheld recently by the United States Supreme Court in Heckler v. Chaney,, 105 S. Ct. 1649 (1985). See also Cutler v. Kennedy, 475, F. Supp. 838, 856 (D.D.C 1979).

In addition, an administrative agency's authority inherent in the administrative process to create general exceptions to statutory requirements has also been upheld in Alabama Power Co. v. Costle, 636 F.2d 323, 357-61 (D.C. Cir. 1980).

Mr. **Weiss**. Dr. Crawford, to get approval from FDA to use a new animal drug in either higher doses or different species, don't you require industrial sponsors to undertake time-consuming and expensive studies to demonstrate its safety and efficacy?

Dr. **Crawford**. Yes.

Mr. **Weiss**. But why bother if you are then just going to allow the veterinarian to use a new animal drug at higher than the approved dose levels or in an unapproved species? You are allowing obviation of the burden placed on the industrial sponsor, and permitting damage, if damage consequently occurs, to be done by the veterinarian.

Dr. **Crawford**. You are quite correct in the fact that adjustments in the dosage does require costly and time-consuming study. We expect that extra-label deviations from those labeled dosages will not be routine and that they will be used carefully and in accordance with human and animal health principles.

One of the reasons that the extra-label use policy has been the policy for such a long time is that if a drug is put on the market at a certain dosage level and then over time resistance to that drug develops so that the dosage level has to be increased, it takes time to prove that the dosage level is effective and that it is safe, and we can't just do it arbitrarily, Mr. Chairman. So one of the reasons that we instituted that policy sometime ago was to allow for emergency adjustments in the dosage or emergency uses in species in the best interest of animal and human health. As you point out, if we allow that to become routine, it could discourage drug manufacturers from seeking to alter their dosage levels, and we have to be very careful about that.

Mr. WEISS. As part of the new animal drug review process, I understand that FDA requires sponsors seeking approval for a new animal drug in an unapproved species to identify the drug's metabolites and then to assess the toxicity of those metabolites as well as the drug itself. Do you assume that practicing veterinarians just automatically know about these matters when they use a veterinary drug in an unapproved species?

Dr. CRAWFORD. No, we do not. These drugs that are used extralabelly are always approved in at least one species. And so we do have some considerable acquaintanceship with the toxicology and pharmacology of the drug. We do not assume that the veterinarian would automatically know that, though.

Mr. WEISS. Mr. Dols, so that the record is clear, please define for us what a metabolite is.

Mr. DOLS. A metabolite is what the animal or the biological system degrades the parent compound to.

Mr. WEISS. So that if you start out with a certain chemical, by the time it works itself through the metabolism of the particular animal, you may have a totally different variation—

Mr. DOLS. Variation or——

Mr. WEISS [continuing]. Compounds?

Mr. DOLS [continuing]. Number of compounds.

Mr. WEISS. In reviewing new animal drugs to assure the safety of milk and edible tissues, doesn't FDA normally require detailed data on the relationship between drug dose and residue levels, as well as on the rate at which residues of an animal drug will deplete in the milk and those tissues?

Dr. CRAWFORD. Yes, we do, Mr. Chairman.

Mr. WEISS. Don't you need these data so you can set safe withdrawal and milk-withholding periods?

Dr. CRAWFORD. Yes.

Mr. WEISS. How does FDA assure that veterinarians know what withdrawal and milk-withholding period to set for drugs they use at unapproved dose levels or in unapproved species?

Dr. CRAWFORD. Well, again, we hope that this—the intention of extra-label policy is that they will be used only in unusual circumstances and that every precaution will be exercised to prevent contamination of food. That is written, as you know, into the policy. And we use the term "exaggerated withdrawal periods."

With respect to meat-producing animals, we have issued a number of advisory opinions for emergency use that would ask the veterinarian to withhold consumption of the meat for 6 months, a time which we have cored through experimental drugs before any data is accumulated on dissolution of the drugs in the tissues.

Mr. Weiss. In an October 21, 1983, letter to an inquiring Member of Congress, FDA acknowledged that "[t]he attending veterinarian has no reliable way to determine adequate preslaughter or milk and egg withholding periods following drug treatment."

[The letter referred to follows:]

√ 230

OCT 2

OCT 21 1983

File
Extra label
discussion

The Honorable Thomas E. Coleman
House of Representatives
Washington, D.C. 20515

Dear Mr. Coleman:

Thank you for your letter of October 14, 1983, on behalf of your constituents Drs. Danny Burns and David Fruen, concerning the Bureau of Veterinary Medicine report entitled, "Bulk New Animal Drug Substances."

We believe your constituents have misread the Bulk Drug Task Force report. Under the provisions of the Federal Food, Drug, and Cosmetic Act, drugs which are not generally recognized as safe and effective by qualified experts are deemed "new animal drugs" and may be marketed only upon the basis of approved new animal drug applications (21 U.S.C. 321(w); 360(a) and (b)). This includes unformulated bulk drug substances which would constitute new animal drugs when formulated into finished dosage forms. To this point in time there have been no procedures and criteria established specifically for submitting new animal drug applications for approval consideration for bulk new animal drug substances to be sold to veterinarians for use in compounding drugs for their private practice. The Task Force report recommended that such procedures and criteria be established to facilitate approvals of bulk drug substances for this purpose.

The Agency is currently considering the Task Force recommendations. If regulations are proposed as recommended, there will be opportunity for public comment on the proposal, at which time your constituents would have such opportunity as well.

The FDA's policy regarding extra-label use of drugs in treating food-producing animals is based upon public health concerns about the widespread promiscuous unapproved use of drugs which impacts upon the safety of the Nations's meat, milk, and egg supply. Many of these drugs result in residues in edible products of treated animals, and there are no adequate analytical methods for use by the United States Department of Agriculture Food Safety Inspection Service in its national monitoring program. The attending veterinarian has no reliable way to determine adequate pre-slaughter or milk and egg withholding periods following drug treatment. Some drugs not approved for any animal use, such as chloramphenicol, break down into toxic metabolites which have not been measured nor have tissue depletion studies been completed. Monitoring for the parent drug is not adequate in many instances.

Page 2 - The Honorable Thomas E. Coleman

Veterinarians have a significant public health role and must exercise their responsibilities appropriately. The FDA is focusing its regulatory activities with respect to drug misuse upon the most flagrant situations. We do not intend to interfere with responsible veterinary practice where individual animal diagnosis and treatment dictates drug therapy for a condition for which there is no approved drug, scrupulous precautions are taken to maintain adequate animal identity, and an exaggerated time period is followed before meat, milk, or eggs are marketed for food. A copy of the policy is enclosed for your convenience.

If we can be of further assistance, please let us know.

Sincerely yours,

Robert C. Wetherell, Jr.
Associate Commissioner
for Legislation and Information

2 Enclosures
Constituent's Letter
CVM Revises Policy on Extra-label

cc: HFN-11(2)
HFW-12
HFV-230
R/D:EBallitch:KM:10/18/83
Init:HHallerman:10/19/83
F/T:mc:101/9/83

Mr. Weiss. You would not disagree with that?

Dr. Crawford. I would not disagree with that.

Mr. Weiss. Does USDA normally monitor all animals for all drug residues, or does it usually monitor for animal drugs used only in species for which such animal drugs have been approved?

Dr. Crawford. They monitor randomly and they do not always monitor just for the species in which the drug is approved.

Mr. Weiss. Well, now, again, perhaps you could check with some of your associates because our information is that, with some rare exceptions, USDA only monitors for drug residues in a species for which the drug has been approved.

Dr. Crawford. These would be the exception. I am not disagreeing with that. But I cannot categorically state that they never monitor——

Mr. Weiss. No, no; not never. But usually USDA only monitors for drug residues in a species for which a drug has been approved. Right?

Dr. Crawford. Right.

Mr. Weiss. So even though USDA does have a national monitoring program, there is generally no way for it to know if unapproved drugs are being used by veterinarians under CVM's extralabel use policy in unapproved species. Only in unusual or exceptional situations would they detect use of an animal drug in an unapproved species. Isn't that correct?

Dr. CRAWFORD. If there is wholesale use of the drug, Mr. Chairman, it is probable that FDA's field forces would detect that. In exceptional circumstances where it does not usually occur, you are absolutely correct.

Mr. WEISS. Doesn't FDA's extra-label use policy, then, increase consumers' exposure to animal drug residues that are likely to go undetected by USDA's national monitoring program?

Dr. CRAWFORD. In reviewing the situation in 1983 and 1984 when we implemented the extra-label drug use policy, Mr. Chairman, what we did was tighten down considerably, as you perhaps know. Prior to that time, the policy of the Food and Drug Administration for veterinarians was, and I quote:

> Veterinarians may use any drug they may legally obtain in their practices in accordance with their professional judgment and as long as they did not cause illegal residues.

When we changed the policy, we tightened down on that considerably. We said no longer could veterinarians have the impunity to use any drug they could legally obtain. They could use only those drugs that were approved in at least one species, and only in emergency circumstances could they deviate from label directions, and then only in a veterinarian/client/patient relationship.

It was a considerable tightening of our policy.

Now, the ultimate in tightening, as you mentioned earlier in your communication with Mr. Drozen, is to forbid any uses other than what is on the label. That would be the ultimate. The problem with that is, where that falls down is that we don't have drugs approved for all indications. And if we strictly enforced an on-label policy, there would in fact be animals dying because they could not be treated. There also would be diseased animals being offered for slaughter because there are those conditions for which no drug exists to treat the animal, in both large animal medicine or food animal medicine and pet animal medicine. So what we do is allow some leeway to the practicing licensed veterinarian in his own practice or her own practice in order to accommodate those circumstances.

So we have a middle-of-the-road approach. We do not have the laxity that characterized the policy prior to 1983 and we do not have the strict interpretation that would prohibit all these uses. So we are somewhere in the middle.

Mr. WEISS. You had indicated, I believe, in the beginning of your testimony, that in descending order of importance, your priorities are: first, the life and health of human beings; second, the life and health of animals; and third, economic costs and benefits. We have developed in the course of this morning's hearing that there are vast numbers of these drugs that you do not even know are being used and whose residues cannot be monitored. While your concern that no drug exists to treat animals' condition may be admirable, you are putting at risk the life and the health of human beings. That is the problem that appears to emerge.

Dr. CRAWFORD. I appreciate that point of view and it is one, as you know, that we have wrestled with a long time. However, in tightening up the procedures in 1983, we actually made less risk to human health by a considerable order of magnitude.

Mr. Weiss. At this point, I want to express my appreciation to our ranking member, my distinguished colleague from Pennsylvania, Mr. Walker. I will now ask him to make whatever comments he may have, or to engage in the hearing in any way that he deems appropriate.

Mr. Walker. Thank you, Mr. Chairman. And I will be brief.

First, Dr. Crawford, my staff informs me that you have been very forthright in response to some tough questions, and we appreciate your willingness to participate in these hearings in that manner and your help to this subcommittee in pursuing this subject area.

Second, I understand that there has been some discussion of memoranda from within the agency that indicate there is a difference of opinion, that some memoranda have been issued and the procedures have not been followed exactly the way somebody would have liked it done.

Maybe you would comment just for the record on at least my impression of that kind of thing, that while it does raise questions, it certainly needs to be addressed in hearings of this type. It also can be a sign of a healthy discourse within an agency, can't it, that in fact people who are pursuing some of these subject areas will have differences of opinion? But the very fact that those subject matters get aired and that there are decisions made creates a healthy climate, in which scientists work and in which appropriate administration takes place.

Dr. Crawford. Yes. Dr. Guest, who is to my right here, and I have managed the Center for Veterinary Medicine the past 7 years. And during that time, we have tried to encourage internal and external discourse. The internal discourse that you refer to basically reposes in individuals that have an alternative point of view in the decision process and sometimes after the decision process, wanting to put on record, at our insistence, the nature of their disagreement, scientific, regulatory, or even research. Those are entered in the record, as they should be, and they also should be heard, and I believe are heard in the Center for Veterinary Medicine.

We have a policy that Dr. Guest and I reserve the right to final decision, because that is what the statute demands, but that we will hear from all individuals. And the persons making alternative points of view do not have the right to prevail; they do have the right to be heard. And that is our operating credo.

Mr. Walker. Let me also congratulate you for that. It does involve the risk of some second-guessing by congressional committees or other outsiders, and I think that that can be healthy from time to time, too. But I think all told, having also served on the Science and Technology Committee, where I get a chance to talk to scientists from a lot of different subject areas, it seems to me that that kind of healthy discourse is precisely what we need in Government laboratories and laboratories across the country.

One other question for you. You were just talking a few minutes ago to the chairman with regard to the leeway that you have decided as a matter of policy to give to veterinarians with regard to certain prescription drugs. The one thing you did not mention, that seems to me to also be a concern that could have a rather large impact on human health would be the development of a fairly large black market in drugs should you try to maintain a stringent policy.

Would you comment on that and the impact that might ultimately have on the health factor in human consumption?

Dr. **Crawford**. Yes. We believe and have direct evidence to show that although we have some deviations that the American veterinary profession stands as a very responsible, very health-oriented group of individuals, perfectly well trained, no doubt the best well trained in the world to deal with these kinds of problems.

A veterinarian, a livestock owner, or even the American public at large is not going to stand by and allow whole herds of animals to die and suffer without a drug. Let's say that the animals are sheep and the same drug is approved in a contiguous species like cattle, that just is not going to happen. If we forbid the use of these drugs extra-labelly, then you are not only going to have a large black market problem, you are going to have an animal welfare problem; and, most of all, you are going to have a human health problem.

For instance, in the case of animals infected with liver fluke disease and other debilitating diseases, all animals that are produced in this country for food find their way into food, in some way, shape, form, or fashion. The greatest public health initiative that I know of anywhere is the current state of animal health in the United States. Healthy animals are less likely to cause so-called zoonotic diseases. The advent of safer, more effective drugs—and I might add that over the last 10 years it has been axiomatic that if a drug is approved recently, and that is, within the last 10 years, it not only is, on the whole, safer; we have an analytical method for it in every case to find its presence in the tissues. It also offers a therapeutic and, therefore, public health advantage. So we try to do our best to streamline the drug process so that we have drugs approved for every indication that there is out there, but we still don't, and it will be a long, long time before we ever do.

In the interim, we have to have an extra-label policy. It is up to us to police it. It is up to us to communicate with the American veterinary profession, State and local authorities, and so forth, in making sure it works as properly as possible.

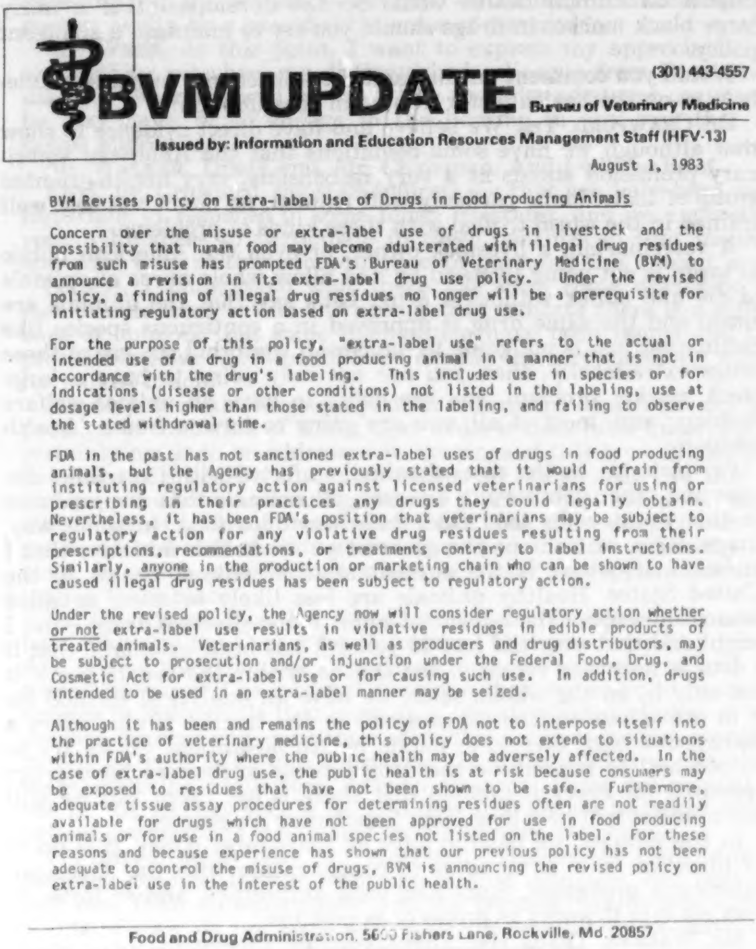
Mr. **Walker**. Thank you. Thank you, Mr. Chairman.

Mr. **Weiss**. Thank you very much, Mr. Walker.

Dr. Crawford, on August 1, 1983, CVM announced that it would take regulatory action against anyone, including veterinarians, for "[any] extra-label use or for causing such use." I assume that you supported that announcement?

Dr. **Crawford**. Yes.

[The announcement referred to follows:]



BVM UPDATE (301) 443-4557

Bureau of Veterinary Medicine

Issued by: Information and Education Resources Management Staff (HFV-13)

August 1, 1983

BVM Revises Policy on Extra-label Use of Drugs in Food Producing Animals

Concern over the misuse or extra-label use of drugs in livestock and the possibility that human food may become adulterated with illegal drug residues from such misuse has prompted FDA's Bureau of Veterinary Medicine (BVM) to announce a revision in its extra-label drug use policy. Under the revised policy, a finding of illegal drug residues no longer will be a prerequisite for initiating regulatory action based on extra-label drug use.

For the purpose of this policy, "extra-label use" refers to the actual or intended use of a drug in a food producing animal in a manner that is not in accordance with the drug's labeling. This includes use in species or for indications (disease or other conditions) not listed in the labeling, use at dosage levels higher than those stated in the labeling, and failing to observe the stated withdrawal time.

FDA in the past has not sanctioned extra-label uses of drugs in food producing animals, but the Agency has previously stated that it would refrain from instituting regulatory action against licensed veterinarians for using or prescribing in their practices any drugs they could legally obtain. Nevertheless, it has been FDA's position that veterinarians may be subject to regulatory action for any violative drug residues resulting from their prescriptions, recommendations, or treatments contrary to label instructions. Similarly, anyone in the production or marketing chain who can be shown to have caused illegal drug residues has been subject to regulatory action.

Under the revised policy, the Agency now will consider regulatory action whether or not extra-label use results in violative residues in edible products of treated animals. Veterinarians, as well as producers and drug distributors, may be subject to prosecution and/or injunction under the Federal Food, Drug, and Cosmetic Act for extra-label use or for causing such use. In addition, drugs intended to be used in an extra-label manner may be seized.

Although it has been and remains the policy of FDA not to interpose itself into the practice of veterinary medicine, this policy does not extend to situations within FDA's authority where the public health may be adversely affected. In the case of extra-label drug use, the public health is at risk because consumers may be exposed to residues that have not been shown to be safe. Furthermore, adequate tissue assay procedures for determining residues often are not readily available for drugs which have not been approved for use in food producing animals or for use in a food animal species not listed on the label. For these reasons and because experience has shown that our previous policy has not been adequate to control the misuse of drugs, BVM is announcing the revised policy on extra-label use in the interest of the public health.

Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20857

Mr. WEISS. And, in fact, I understand that you defended that policy to the American Veterinary Medical Association (AVMA) by observing that "we cannot detect the presence of unapproved drugs in meat, milk, or eggs." Is that correct?

Dr. CRAWFORD. Correct.

[Dr. Crawford's October 13, 1983, memorandum to AVMA's Executive Board follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

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OCT 13, 1983

MEMORANDUM TO: THE EXECUTIVE BOARD OF THE
AMERICAN VETERINARY MEDICAL ASSOCIATION

SUBJECT: Extra-Label Use of Veterinary Drugs

Gentlemen:

It is my understanding you will shortly be considering the problem of the ethical usage of veterinary drugs. I am writing each of you so that the special concerns of FDA's Bureau of Veterinary Medicine may be brought to your attention. Let me first of all ask that you note the attachments to this letter:

(A) BVM Talk Paper on the Extra-Label Use of Veterinary Drugs. This document states the position of FDA under the Federal Food, Drug, and Cosmetic Act. At times in the past, BVM had exercised regulatory discretion in asserting that veterinarians could employ any drug that could be legally obtained in the private practice of veterinary medicine provided he/she assumed responsibility for adverse reactions and adulteration of edible tissues. Exploitation of that policy has forced the change described in Attachment (A). The former policy allowed a legal haven not only for unethical practitioners but for illegal drug distributors that either were veterinarians or that employed veterinarians to legitimize the diversion of unapproved products for use in food-producing animals. The gravity of our concern is underscored by the fact that, with few exceptions, we cannot detect the presence of unapproved drugs in meat, milk, or eggs. This and the evidence that drug misusage is increasing, dictated the policy change -- a change designed to facilitate prosecution of the flagrant violator.

(B) Clarifying Statement. Much appreciation should be accorded AVMA for assembling representatives from 13 livestock agriculture and professional organizations in Schaumburg on September 27th for the purpose of clarifying the policy. Attachment (B) represents a statement of clarification that BVM can endorse because it is consistent with the law and it will allow us to take the necessary steps to correct the current situation.

(C) Address by Gerald B. Guest, DVM, Deputy Director, Bureau of Veterinary Medicine, FDA, at the Academy of Veterinary Consultants Meeting, Amarillo, Texas, June 3, 1983.

(D) Address by William B. Bixler, VMD, Associate Director for Voluntary Compliance and Operations, Bureau of Veterinary Medicine, FDA, at the American Veterinary Distributor's Association Meeting, Lancaster, Pennsylvania, July 15-16, 1983. (see especially pages 13-25).

(E) Address by Max L. Crandall, DVM, Associate Director for Surveillance and Compliance, Bureau of Veterinary Medicine, FDA, at the National Feed Ingredient Association Meeting, Williamsburg, Virginia, October 3, 1983.

Attachments (C), (D), and (E) are particularly important because the nature of the drug misuse problem is explained. The pattern of drug misuse, if allowed to further degenerate, will very likely lead to public embarrassment and to a general concern about the safety of the food supply. I believe the FDA response is not only justified but wholly necessary. Only the veterinary profession itself, however, can outline the ethical standards of drug usage. That is why your deliberations are particularly welcome at this time.

Lester M Crawford

Lester M. Crawford, DVM
Director, Bureau of
Veterinary Medicine

cc: Dr. D. T. Albrecht
Dr. J. S. Gloyd
Dr. D. A. Price
Dr. C. B. Randall
Dr. C. R. Rigdon

bcc: Dr. Guest, HFV-2
Dr. Bixler, HFV-3
Dr. Baldwin, HFV-100
Dr. Crandall, HFV-200
Dr. Norcross, HFV-300
Dr. Teske, HFV-500

Mr. WEISS. Why, then, did you change that policy in January of 1984?

Dr. CRAWFORD. We had a large amount of dialogue about the policy, and at the insistence of some 27 different groups, consumer groups, livestock production groups, veterinary medical groups and so forth, a meeting was convened to hear their complaints. This was in September of 1983.

At that meeting—and for the record, immediately afterwards—there was a listing of the various disease states in animals, including some diseased conditions transmissible to man, that could not, under the strictest interpretation of the extra-label use policy, be treated. The feeling was that this would pose a threat to animal health and to human health, and that FDA had, in its zeal to police public health, overreached the boundaries that it should have reached and that some modification was needed. The modification took the form of a set of guidelines called the Veterinarian/Client/Patient Relationship, or VCP. And what that means is that in those circumstances where deviations from the label have to take place, these should be allowable, with FDA's concurrence, if the following conditions are met.

The first condition is that the veterinarian had to have a fiduciary relationship with the animal herd; that is, they actually had to be in charge of the health of that herd.

The second thing is that the veterinarian had to be on call so they could attend to the herd in case something happened otherwise. And then, thirdly and finally, the veterinarian had to assure that no risk to animal or human health occurred as the result of the occasional extra-label usage.

Hearing the modifications and realizing that one of the spin-off benefits of introducing the original policy was to get the attention of individuals in this area and, also, realizing that strict enforcement of a "use only as the label demands" policy was not feasible, we acceded to the compromised position in January of 1984.

Mr. **Weiss**. Our information indicates that the extra-label use policy compromise was drafted by the Association. Is that correct, the——

Dr. **Crawford**. It was drafted in concert with the Center for Veterinary Medicine. Dr. Guest and I were involved and two other people from the Center for Veterinary Medicine. It was a common effort. It also involved the concurrence of the 26 other groups that I mentioned. So it is not correct to say that it was entirely the work of the American Veterinary Medical Association.

Most authorities—most press reports of the compromise accord greatest credit to the American Association of Bovine Practitioners.

Mr. **Weiss**. We will have entered into the record some exchange of correspondence in January 1984 which indicates that FDA, in fact, adopted language which was submitted by the Veterinary Medical Association. You might want to review that exchange of correspondence.

[AVMA's January 6, 1984, letter to Dr. Crawford, and Dr. Crawford's January 13, 1984, response follow:]

AMERICAN VETERINARY MEDICAL ASSOCIATION
930 NORTH MEACHAM ROAD · SCHAUMBURG, ILLINOIS 60196 · PHONE 312/885-8070

January 6, 1984

Dr. L. M. Crawford, Director
Bureau of Veterinary Medicine
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Crawford:

AVMA acknowledges the role of the veterinary medical profession and livestock agriculture in the protection of public health through the responsible use of animal drugs. Further, the AVMA favors FDA's taking corrective action when the flagrant misuse of a drug product has the potential for causing harmful drug residues in food for man. To those ends, the Association intends to cooperate with FDA in its efforts to reinforce proper drug usage, minimize the occurrence of drug residues, and disseminate the latest information on the pharmacology of selected over-the-counter and prescription veterinary drugs.

AVMA also favors the development of new approvals for needed veterinary drugs, particularly those intended for use in minor species or in major species for minor uses. AVMA will participate in liaison among FDA, the land-grant university system, and the pharmaceutical industry in this regard. FDA's approved list of veterinary drugs does not include drugs for every major condition known to affect animals. This quite naturally stimulates the use of untested and/or unapproved compounds. More efficiency in the FDA approval process and more activity by the industry in drug development will help to alleviate this situation; moreover, a broader, more comprehensive list of approved drugs will provide the veterinary profession with a safer, more effective armamentarium and the public with a safe, efficiently-produced supply of meat, milk, and eggs.

Even though you found it unacceptable, we appreciated your consideration of the proposed revision of FDA's policy on extra-label drug use that we transmitted to you following our Executive Board meeting on October 29, 1963. On recommendation of AVMA's ad hoc Committee on Extra-Label Use of Drugs, our Board of Governors now offers a further revision, attached hereto, which they believe merits FDA adoption.

continued...

We anticipate your favorable response.

Sincerely,

Richard B. Fink
R. B. Fink, D.V.M., Chairman
Executive Board

RBF/cap

Encl.

REVISED AVMA RECOMMENDATION FOR FDA POLICY ON USE OF DRUGS IN FOOD PRODUCING ANIMALS

December 15, 1983

Under current FDA regulation, (21 CFR, &201.105), the Bureau of Veterinary Medicine is authorized to restrict the sale and distribution of an animal drug "only to or on the prescription or other order of a licensed veterinarian for use in the course of his professional practice." This restriction is imposed when the Bureau finds that, "because of toxicity or other potentiality for harmful effect, or the methods of its use, (the drug) is not safe for animal use except under the supervision of a licensed veterinarian"; adequate directions for use by non-veterinarians cannot be written, and the drug could not otherwise be approved for marketing.

The Bureau of Veterinary Medicine has found instances in which prescription veterinary drugs have been distributed to non-veterinarians "by or on the order of a licensed veterinarian," but this has taken place under circumstances that the Bureau believes are beyond the intended scope of "the course of the (veterinarian's) professional practice." In other instances, the Bureau has become aware of distribution of other drug substances not approved for food animal use and the use of these drugs in the absence of a veterinarian-client-patient relationship.

The agency does not intend to interfere with responsible veterinary practice where diagnosis and treatment dictate drug therapy for a condition for which there is no approved drug or for which approved drugs or dosages have been found to be clinically ineffective. However, scrupulous precautions shall be taken to maintain adequate identity of the treated animals and to assure that appropriate, extended time periods elapse before meat, milk, and eggs are marketed for human food. The agency acknowledges, therefore, that the prudent use of FDA-approved drugs for extra-label purposes is necessary in the course of veterinary practice within the framework of a bona fide veterinarian-client-patient relationship. Furthermore, the agency will take necessary action to prevent, stay, or curb the distribution and use of drugs not approved for use in food animals in the absence of a veterinarian-client-patient relationship.

The wide diversity of definitions of professional practice in the state laws regulating the practice of veterinary medicine makes it impossible for FDA to rely on those definitions to operate a uniform and equitable national regulatory program. The purpose of this policy statement is to provide FDA's interpretation of the phrase "for use in the course of his professional practice," and to further define the veterinarian-client-patient relationship as it relates to that practice.

A prescription veterinary drug cannot be used safely except under the supervision of a licensed veterinarian because of the drug's potential harmful effects or the method of its use. Thus the phrase "for use in the course of his professional practice" necessarily implies that the veterinarian is supervising the use of the prescription drug.

In order for the veterinarian to supervise the use of a prescription drug or drugs not approved for food animal use, an appropriate veterinarian-client-patient relationship must exist.

An appropriate veterinarian-client-patient relationship will exist when:

(1) The veterinarian has assumed the responsibility for making medical judgments regarding the health of the animal(s) and the need for medical treatment, and the client (owner or other caretaker) has agreed to follow the instructions of the veterinarian; and when

(2) There is sufficient knowledge of the animal(s) by the veterinarian to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s). This means that the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of an examination of the animal(s), and/or by medically appropriate and timely visits to the premises where the animal(s) are kept; and when

(3) The practicing veterinarian is readily available for follow-up in case of adverse reactions or failure of the regimen of therapy.

January 13, 1984

R. B. Fink, DVM
Chairman
Executive Board
American Veterinary Medical Association
930 North Meacham Road
Schaumburg, Illinois 60196

Dear Dr. Fink:

I am in receipt of your letter dated January 6, 1984 in which you attach the document titled "Revised AVMA Recommendation For FDA Policy On Use Of Drugs In Food-Producing Animals." I have read and am conversant with that document and find it acceptable in all particulars.

The language is somewhat different from that expressed in my address to the American Association of Bovine Practitioners (AABP) on November 30, 1983 (copy attached), but I am persuaded the intent is essentially the same and that the AVMA statement provides better guidance to the veterinary medical practitioner. Therefore, BVM-FDA will substitute your wording for that previously stated by the Bureau in the August 1, 1983 statement entitled "Extra-Label Use Policy" and in the November 30, 1983 address to AABP.

This decision will be announced externally through a forthcoming BVM UP-DATE and internally through the usual headquarters and field channels. AVMA may, of course, utilize all or part of this letter in communicating this decision to the profession and to other interested groups.

I very much appreciate the resourcefulness and commitment of AVMA in dealing with this matter. Much progress has been made during the past six months in defining the essentials of the veterinarian-client-patient relationship and in fostering a more responsible attitude regarding veterinary drug usage in this country. For that you deserve the gratitude of the American public as well as that of the profession you serve so well.

Sincerely yours,

Lester M. Crawford, DVM, PhD
Director, Bureau of
Veterinary Medicine

Enclosure

cc: Dr. M. Decker, AVMA
bcc: Associate Directors, BVM (w/copy of incoming ltr)

Dr. **Crawford**. I would be pleased to review it, Mr. Chairman, and thank you. However, I am knowledgeable that it was a joint effort and not a unilateral effort.

Mr. **Weiss**. I understand that you and the agency have been working very hard to increase the number of new animal drug approvals each year. How many new animal drugs have been approved each year from 1981 to the present?

Dr. **Crawford**. 1982, we had 25 major new animal drug approvals, including 11 new entities. This would be new drugs not approved before. In 1983, we had 35 major new animal drug approvals, including, I believe, 7 new entities. And then last year, 1984, we had 34 new animal drug approvals, with, I believe, 5 new entities. So the new entities actually have been declining the last 3 years, but the numbers of new animal drug approvals have been maintaining the same high level of 1982.

Now, in 1981, we had fewer approved than in 1982, and still fewer in 1980.

Mr. **Weiss**. In a May 1983 speech before the Animal Health Institute, you cited the large number of new animal drugs that had recently been approved as a major agency achievement. Isn't that correct?

Dr. **Crawford**. Yes.

Mr. **Weiss**. Dr. Beaulieu, however, has reviewed the approval of four veterinary drugs in 1982 and 1983 and found that each presented serious safety and/or manufacturing problems. Dr. Beaulieu wrote, "As [Scientific Evaluation] speeds its approval process, there is an apparent increase in the need for [Division of Surveillance] to pick up the pieces."

[See Dr. Beaulieu's memorandum prepared for a July 12, 1984, CVM management meeting, which is in the record.]

Mr. **Weiss**. Is it unusual for CVM to encounter so many problem drugs in so short a time after they were approved?

Dr. **Crawford**. Dr. Beaulieu's job—let me go back to organization very briefly. The job of the new animal drug evaluation area is to speed these drugs through as safely and quickly as is legitimate. Once they are on the market, it is the job of Dr. Beaulieu to survey them and monitor them and, in effect, to second-guess the approval process. It is sort of a healthy tension, we believe, between the two areas.

We found over time that if the drug is approved in new animal drug evaluation, people become attached to the drug. They are proud of its introduction and they want to follow it almost as a career move. So we switch consideration of the drug from that group to the other group once it gets on the market.

Dr. Beaulieu correctly cited four drugs, and I believe two had some problems associated with them. And he wondered, and I think quite legitimately, is the improved drug approval process overlooking some of these things like dissolution problems and so forth. And I think he was quite correct to point that out. I think it is something that we need to always insert in terms of quality control.

Mr. **Weiss**. I understand there were problems with each of those four.

Dr. **Crawford**. What are the drugs, if I may ask?

Mr. **Weiss**. Four. And he found that each of those four drugs presented serious safety and/or manufacturing problems. And——

Dr. **Crawford**. I am not aware of the safety problems being serious. I think there were some manufacturing problems.

Mr. **Weiss**. Ivermectin, I'm told by staff, was one of those that presented a safety problem.

Dr. **Crawford**. That was a problem involving injection site problems in horses, which did result in some horse deaths. And to the horse, those, of course, were serious problems and resulted in the withdrawal of that product from the market. That is correct.

Mr. **Weiss**. The point Dr. Beaulieu is making is that as the approval process speeds up, problems which could be otherwise spotted before approval are more likely to occur. We must rely more heavily on post-approval surveillance to identify these problems.

Dr. **Crawford**. That is an important consideration. There are two ways of looking at that. And I would always charge Dr. Beaulieu, or whoever serves in his position, to continue to raise those kinds of questions.

My view of it is that within the spirit of the law it is incumbent upon us at FDA to approve the drugs as efficiently as possible, if they are going to be approved, and not delay the process without sufficient reason. I also believe that the new generation of drugs are, for the most part, safer and more effective and they take the place of older, more toxic drugs in many cases. But we always ought to have that reexamination that you have characterized as being one of the responsibilities of Dr. Beaulieu.

Mr. **Weiss**. How do CVM resources that are directly devoted to approving new animal drug approvals compare to those allocated for postmarket surveillance?

Dr. **Crawford**. Well, within headquarters, we have slightly over 100 personnel involved in the drug approval process and we have slightly under 100 involved in the surveillance/compliance part. We can give you those exact figures. They are roughly 103 in the preapproval process and approximately 89 in the postapproval process.

Mr. **Weiss**. We have a document from Dr. Beaulieu in which he states that "approximately 43% of CVM resources are directly devoted to approving NADA's," while approximately 3% of CVM resources are directly devoted to monitoring NADA's."

[The document referred to, which was prepared for a January 24, 1984, briefing with FDA's Acting Commissioner, follows:]

MONITORING MARKETED ANIMAL DRUGS & DEVICES

PMS 65

APPROXIMATELY 43% OF CVM RESOURCES ARE DIRECTLY DEVOTED TO APPROVING NADA'S (SE + HFS)

APPROXIMATELY 3% OF CVM RESOURCES ARE DIRECTLY DEVOTED TO MONITORING APPROVED NADA'S (PART OF DS)

GIVEN THIS ALLOCATION OF RESOURCES, WE MUST GET THE APPROVALS RIGHT THE FIRST TIME, EVEN IF THIS MEANS DELAYING SOME APPROVALS. WE CANNOT DEPEND ON THE 3% TO CORRECT SITUATIONS POST-APPROVAL WHICH REALISTICALLY COULD HAVE BEEN RESOLVED PRE-APPROVAL.

CONSIDER THE RELATIVE EXPENDITURE OF RESOURCES ASSOCIATED WITH STANDING FIRM DURING THE PREAPPROVAL PROCESS WHEN THE FIRM WANTS TO GET ON THE MARKET, VERSUS CORRECTING THE SITUATION POST-APPROVAL WHEN WE USUALLY HAVE NO BARGAINING POWER AT ALL.

ADMINISTRATIVE PROCEDURES ASSOCIATED WITH CORRECTING DEFECTS IN APPROVED PRODUCTS OR NADA'S ARE SO CUMBERSOME AND RESOURCE INTENSIVE THAT THEY DO NOT SERVE AS A VIABLE DETERRENT TO THE MARKETING OF OBJECTIONABLE PRODUCTS.

OBJECTIONABLE = MANUFACTURING DEFECTS, EXCESSIVE ADR'S, INADEQUATE LABELING, VIOLATIVE PROMOTIONAL MATERIAL, SIGNIFICANT DATA DEFICIENCIES.

Dr. CRAWFORD. That is incorrect. We have the two major divisions in CVM. One is called the Office of Surveillance and Compliance; there are 80-some-odd people in there. Then we have the Office of New Animal Drug Evaluation and there are 103 people in there.

Within the Office of Surveillance and Compliance, there are three divisions: Dr. Beaulieu's division, which is Surveillance, is one of those divisions. The number "three" that he mentions, I am not sure; that may be a branch under him. But our overall commitment to Surveillance and Compliance is nearly the same as it is in New Animal Drug Evaluation.

Now, if you add the field forces in there, that is, the number of our personnel that we devote to field effort, then you have more people working in Surveillance and Compliance than you do in New Animal Drug Evaluation.

Mr. WEISS. Dr. Crawford, does the center have an operational computerized system for monitoring reports of adverse effects associated with the use of veterinary drugs?

Dr. CRAWFORD. Yes. We have a system called the VDERP, or Adverse Drug Reaction Program.

Mr. WEISS. And when was that instituted?

Dr. CRAWFORD. It was instituted, Mr. Chairman, I believe the first contracts were awarded in 1975. Now, the attempts to computerize it were much more recent. It was done by hand in the form of a quarterly report in the mid-1970's and up to comparatively recent times. To design a computer program for it began about 2 years ago.

Mr. WEISS. Is it now operational?

Dr. CRAWFORD. It is not completely operational. It is not at the point that we want it to be. Ideally, we would have a program that we would be on line with, say, veterinary medical hospitals and industry people, as well as anyone else who is interested. And they could actually dial in and get the numbers of adverse reactions with all the drugs. We are not to that point yet.

Mr. WEISS. What does it do at this point?

Dr. CRAWFORD. What it does now is, we enter the data in essentially by hand, into the computer program, and then we are able to, within the center, recall some of that information. What it does not do, it is not externally available and it is not available except to those individuals who are working within that particular area. And if I, for instance, want a report on a certain drug, they have to give me a hard copy. It does not show up on the computer that is on my desk. So it is in the very early stages of development.

It is a hard program to develop because you would like for it to be cross-hatched. You would like it to be able to say how many reactions this drug has caused in all different species, and have that come out in an electronic fashion. And we have had difficulties developing the program, great difficulties.

Mr. WEISS. And you have an outside consultant doing that for you?

Dr. CRAWFORD. We have an outside contract. Perhaps I—we could have Dr. Guest now mention our efforts?

Mr. WEISS. Please.

Dr. GUEST. We do, in various ways, attack the automation of data. Automation of data for us and for everybody I've talked to is always a painful, painful kind of a thing because you always expect it to do more than it can really do for you, sooner than you can hope for it to happen.

We have used in the adverse drug reaction area outside consultants as well as our own in-house people, and then we have a cadre of people who are assigned to the Public Health Service there in the Parklawn Building who have helped.

We have two systems in adverse drug reactions. We have the system whereby we receive information from veterinary colleges and teaching hospitals, through the contract that Dr. Crawford is talking about, and then we have other systems where veterinarians have input. We are probably farther along with the contract with veterinary colleges and teaching hospitals than we are with the latter system which I mentioned. But we have—to answer your question more directly, yes; we have had various amounts of help, both outside and inside the center.

Mr. WEISS. When do you think it will be operational and can perform the bulk of what it is that you would expect from such a system?

Dr. GUEST. Well, my information is that we are well along in the contracting system, probably to a point where we are now able to get good usable data. The other system, we seem to have the program on line. It is a matter now of getting all the data over what amount of years that we want in there. I would predict that we are probably a year to 18 months away from having a system that we would reasonably be happy with.

Mr. WEISS. Just to get some idea, how many adverse reaction reports would you have received, say, in 1984, from veterinarians?

Dr. GUEST. Mr. Chairman, I don't have those numbers at my fingertips. The majority of our adverse drug reaction reporting comes from industry sources, that is, veterinarians reporting them to the industry, the industry then reporting them to us. So to tell you precisely how many come from veterinarians, I am not sure.

We also get quite a large number from veterinary colleges and teaching hospitals. We do not get reports directly from veterinarians to the extent we would like to have it. I can furnish you those numbers, though, for the record.

Mr. WEISS. Would you, for the record, provide those numbers for, say, the last 3 years. Please supply the numbers for colleges and for the hospitals as well as the industrial sources.

Dr. GUEST. Mr. Chairman, did you say 3 years?

Mr. WEISS. Yes.

[The information requested follows:]

DRUG EXPERIENCE REPORT ADVERSE DRUG REACTIONS

	DERs	ADRs	Total
Fiscal year 1983:			
1st quarter	538	343	881
2d quarter	568	263	831
3d quarter	807	429	1236
4th quarter	552	236	788

DRUG EXPERIENCE REPORT ADVERSE DRUG REACTIONS—Continued

	DERs	ADRs	Total
Total	2,465	1,271	3,736
Fiscal year 1984:			
1st quarter	514	264	778
2d quarter	468	208	676
3d quarter	765	368	1133
4th quarter	612	284	896
Total	2,359	1124	3,483
Fiscal year 1985:			
1st quarter	476	291	767
2d quarter	383	228	611
3d quarter	751	308	1059
Total	1,610	827	2,437

Mr. **Weiss**. According to FDA files, when FDA approved carbadox for use in swine in 1972, it knew that it was a carcinogen. On January 8, 1979, FDA's Cancer Assessment Committee concluded that a metabolite of the drug is an even more potent carcinogen than the drug itself.

[The memorandum of the Cancer Assessment Committee's January 8, 1979, meeting follows:]

MEMORANDUM OF CONFERENCE

Date: January 8, 1979

Place: Bureau of Foods

Purpose: Meeting of the Cancer Assessment Committee

Subject: 1) 2-Amino-5-nitrothiazole
2) Carbadox

Participants:

Cancer Assessment Committee Members

Dr. W. Flamm, HFF-152
Dr. M. Weinberger, HFF-130
Dr. S. Shibko, HFF-195
Dr. R. J. Lorentzen, HFF-180
Dr. R. Livingston, HFF-144
Mr. R. Brown, HFF-110

Others

Dr. T. Sulkowski, HFF-144
Dr. N. Weber, HFF-144
Dr. B. Jackson, HFF-180
Dr. R. Osterberg, HFF-180
Dr. T. Farber, HFF-180
Dr. P. Sundaresan, HFF-180
Ms. K. Hogye, HFF-110
Dr. D. Jones, HFF-335

A summary of the data in DHEW Publication No. (NIH) 78-1303 on the bioassay of 2-amino-5-nitrothiazole for possible carcinogenicity was presented by Dr. Osterberg. In the studies reviewed, the lesions of interest were in the hematopoietic system and the incidence of these tumors was statistically significant in male rats only. A discussion ensued about the possible involvement of oncogenic viruses in the production of lymphomas and leukemias. It was concluded that a viral etiology for these lesions would be difficult to demonstrate, particularly for the rat; in this vein, the Agency's policy was stressed, to wit the assumption of direct carcinogenic culpability in the absence of knowledge that the test compound is exclusively producing promotional or co-carcinogenic effects.

Other issues relating to the induction of hematopoietic tumors were also discussed. The calulations for determination of statistical significance of these tumor incidences were explained in more detail for the Committee. After these considerations were aired, the Committee concluded that, while the Fisher 344 rat may not be the most appropriate model for assaying the induction of tumors of the hematopoietic system because of relatively high spontaneous incidences, and while the potency of the response is rather unimpressive, the significance of the data cannot be ignored and 2-amino-5-nitrothiazole is a carcinogen in male rats. It was suggested the adjective "weak" should be included in the description, but it was explained that for animal drugs, the SOM document specifically takes potency into account. At this point, it was stated that the acetyl derivative of 2-amino-5-nitrothiazole was the actual regulated drug.

It is known, however, that the deacetylated compound is present as a residue in the tissues of treated food animals. The acetyl derivatives has apparently not been tested, but the Committee concluded it was suspect because, apart from easy _in vivo_ conversion to free amine by hydrolysis, acetylated aromatic amines have sometimes been shown to be more potent carcinogens than their free amine analogs.

A summary of a number of oncogenicity studies on carbadox and its metabolites was presented by Dr. Jackson. One of the metabolites, desoxycarbadox, clearly produced high incidences of hepatocellular carcinoma in the rat, a very rare spontaneous tumor in this species. The Committee quickly assessed desoxycarbadox to be a hepatocarcinogen in the rat. The parent drug, carbadox, also produced lesions in the liver. However, the incidence of malignancies was quite low. The association of benign nodular hyperplasia with drug treatment and in proximity to the hepatocellular carcinomas was concluded to be strong evidence for the carcinogeniicty of carbodox. The committee concluded that all the data taken together implicate carbadox to be a~~n~~, albeit weaker than desoxycarbadox, heptocarcinogen in the rat.

RJLorentzen:pae:1/17/79

Mr. **Weiss**. Does FDA have a method for detecting residues of this drug and its carcinogenic metabolite down to the "safe" level set by FDA as corresponding to a cancer risk of 1 cancer in 1 million population?

Dr. **Crawford**. Excuse me just 1 minute.

[Pause.]

Dr. **Crawford**. We have a method, Mr. Chairman. I conferred with Mr. Dols here, who may wish to elaborate; a part that goes down to 30 parts per million—excuse me—30 parts per billion for carbadox. For levels lower than 30 parts per billion, we cannot reliably detect. We would like to have a better method for this compound, but that is the limitation of the method at the present time.

Mr. **Weiss**. Is my understanding correct that the "safe" level set by FDA, Mr. Dols, is that which corresponds to a calculated cancer risk of 1 cancer in a 1 million population?

Mr. **Dols**. The present tolerance that is in the—that is published is 30 parts per billion. We have never changed that. What that corresponds to in risk, I do not know.

Mr. **Weiss**. Well, could you try to submit that to us for the record?

Mr. **Dols**. Yes, I will.

[The information requested follows:]

The "tolerance" of 30 ppb is based on the official assay method for quinoxaline -2-carboxylic acid a non-carcinogenic metabolite of carbadox. The carbadox parent compound rapidly metabolites into this metabolite and another metabolite which has been shown to be carcinogenic in laboratory animals. Since carbadox was approved prior to the Agency's proposed risk assessment procedures and the one in one million acceptable risk policy, we have not quantitated the risk associated with the residues of carbadox or the carcinogenic metabolite remaining in the animal at the 70-day withdrawal. However, it is likely that because of their more rapid depletion, these compounds would be at levels many magnitudes below the 2-carboxylic acid and of neglible risk at the required withdrawal time.

Mr. **Weiss**. On September 29, 1981, Dr. P.R. Sundaresan, Food Animal Additives Evaluation Branch, recommended that FDA initiate market withdrawal proceedings against carbadox.

[Excerpts from Dr. Sundaresan's September 29, 1981, memorandum follow:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date September 29, 1981

From Dr. P. R. Sundaresan, Ph.D. P.R. Sundaresan 9/30/81
Food Animal Additives Evaluation Branch (HFF-154)

Subject Human Safety Evaluation - Carbadox - Pfizer, Inc.

To Director, Food Animal Additives Staff (HFF-350)

Thru: Dr. Theodore M. Farber
Chief, Food Animal Additives Evaluation Branch (HFF-154)

The Program Director (Animal Derived Food Safety) has requested a detailed evaluation of the human safety data for the animal drug Carbadox as well as a discussion of the safety of this compound. In addition, the Division of Toxicology, based upon this evaluation, is to advise the Program Director whether the safety concerns are sufficient to warrant a withdrawal action against carbadox and to recommend alternatives if it were decided not to take a withdrawal action against the product.

The following analysis and comments are offered for your consideration. This report is a product of reevaluation of data submitted during the past many years to the Bureau by the sponsor. A summary of the position of DT and the safety of carbadox can be found on pages 80-84 followed by our recommendations for alternative courses of action in lieu of immediate withdrawal action against the compound.

Introduction

Carbadox is an antimicrobial drug and is currently used in the feed of swine for growth promotion and improved feed efficiency at 10-25 gms/ton. It is also used for control of swine dysentery and of bacterial swine enteritis and for increased rate of weight gain and improved feed efficiency at 50 gms/ton (0.0055%). The limitations restrict the use of this drug to swine weighing not more than 75 lbs in body weight and the drug is not to be mixed in complete feeds containing less than 15% crude protein. In addition, the agent is not to be fed to swine within 10 weeks of slaughter, thus providing a practical withdrawal period of 70 days.

READEX
FICHE

The following summarizes these reviews:

1. DER-92-955:

The majority of these studies were either insufficient in design or reporting for making any clear scientific judgement, especially with regard to the definition of a negative finding. Just one example is the study in which rats were fed carbadox or desoxycarbadox for varying periods up to 300 days. One portion of this study involved testing urine from these (as well as untreated) animals in a standard Ames' test. The urine from untreated animals gave a response which was more than twice the solvent control (i.e. a defined positive), thus confounding any interpretation of the data on urine from treated animals. (Rat urine is not rountinely found to be positive in an Ames' test).

2. Journal Articles

Carbadox has been shown to be mutagenic in a number of different assays. In three independent studies increases in mutations were detected in both TA98 and TA100 without activation. Additionally carbadox induced gene mutations in *E. coli* and *Klebsiella pneumoniae*, was positive in the *B. subtilis* Rec-Assay (DNA repair), was positive in the mouse micronucleus test and caused increased chromosome aberrations in an *in vitro* mouse cytogenetics assay (Negishi *et al*. 1980; Ohta *et al*. 1980; Oud *et al*. 1979; Shirasu *et al*. 1978; Voogd *et al*. 1980).

F. Carcinogenicity Studies

1. 2 Year Chronic Study on Desoxycarbadox and Carbadox

Report #/Date/Ref:	DER 41-061 Vol. 5/8-15-78/DT review of Dr. P. R. Sundaresan
Petitioner:	Pfizer
Laboratory:	MB Research Laboratories, Inc.
Test Substances:	a. Desoxycarbadox Lot # 7291-224-1F b. Desoxycarbadox Lot # 8735-171-1 c. Carbadox
Species/Strain:	Rat/Charles River crl:COBS(SD)BR

Duration:	335 days
Number/Sex/Group:	14
Dose Levels:	(1) 0(control) (2) 25 mg desoxycarbadox (Lot 7294-224-1F)/kg/day (3) 25 mg desoxycarbadox (Lot 8735-171-1)/kg/day (4) 25 mg carbadox (Lot 47250)/kg/day (Positive control)
Route of Administration:	In diet
Administration:	The concentration of the compound in the meal was calculated based on the body weight and food consumption of the preceding week. The concentration was to approximate an intake of 25 mg/kg/day for each compound.

Observations

Toxic Signs:	Animals inspected twice daily; also palpated for masses monthly
Survival:	Determined twice daily
Body Weight and Food Comsumption:	Recorded weekly until 38th week and then every other week
Necropsy:	Performed on all animals; animals found moribund were killed. Gross and microscopic examination of all major tissues, organs and all gross lesions noted in killed animals as well as in animals found dead, when possible.

Interim Sacrifice: Four animals per group were sacrificed after day 30 while 2 per group were sacrificed at 2,3,6 and 10 months after treatment.

Histopathology: Performed on all animals except those that were lost due to autolysis.

Tissues Examined: Skin, subcutaneous tissue, lung and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenals, thyroid, parathyroid, testes, prostate, brain, uterus, mammary gland and ovary.

Results:

Body Weights: A significant decrease in weight gains of both males and females in carbadox-treated animals when compared to controls was noted. In desoxycarbadox-treated rats, the weight gains were comparable to controls up to 28 weeks of treatment. However, beginning from the 28th week, the weight gains in these animals were significantly less than their respective controls.

Histopathology: In the interim sacrifices (1, 2, and 3 months after treatment) there were no significant gross or microscopic lesions. At the six months sacrifice, one animal receiving desoxycarbadox (CP-17,056) had a rather large area of acute hepatic necrosis. Hepatic damage was observed in one animal which died after receiving CP-17,056 for 8 months.

At 10 months after treatment all 4 rats receiving CP-17,056 showed multiple nodular lesions throughout all lobes of the liver. These were characterized as hepatocellular carcinomas. The two rats receiving carbadox (GS-6244) had hepatic necrosis and areas of nodular hyperplasia.

After 11 months of treatment, the livers of all rats receiving CP-17,056 had nodular lesions characterized as hepatocellular carcinomas. All the rats receiving carbadox had nodular hyperplasia in the liver except two female rats which had hepatocellular carcinomas.

The incidence of hepatocellular carcinomas in males and females was as follows:

control	0/15 (0%)
Desoxycarbadox (Lot 7924-224-1)	14/14 (100%)
Desoxycarbadox (Lot 8735-171-1)	15/15 (100%)
Carbadox	2/8 (25%)

Conclusions: This study has clearly demonstrated that desoxycarbadox is a potent hepatocarcinogen. Both lots of desoxycarbadox tested at 25 mg/kg/day produced hepatocellular carcinomas in 100% of the surviving animals. In addition, both lots of desoxycarbadox caused hepatic necrosis in 2 animals sacrificed after 6 1/2 and 8 months of treatment. The study had to be terminated after 11 months of treatment. Furthermore, this study has demonstrated that carbadox at a level of 25 mg/kg/day is also carcinogenic after 11 months of treatment as evidenced by the incidence of hepatocellular carcinomas in 2 out of 8 female animals. In comparison, no significant liver lesions appeared in control rats at the termination of the study.

2. "A Twenty-Six Month Chronic Toxicity Study of GS-6244 in rats - Dose Levels of 100, 50, 25, 10, 5 or 0 mg/kg"

Report #/Date/Ref:	NADA 41-061/Vol. 10/ 6-10-70/Reviewed by S. H. Frazier
Petitioner:	Pfizer
Laboratory:	Pfizer
Test Substance:	Carbadox
Species/Strain:	Rat/Charles River Crl: COBS(SD)BR
Duration:	780 days
Number/Sex/Group:	10
Dose Levels:	0(control) 5, 10, 25, 50 and 100 mg/kg/day
Route of Administration:	in diet
Administration:	The test substance was mixed with the feed weekly. Symptomatology, body weight

	and food consumption were recorded weekly and drug levels adjusted accordingly

Observations

Toxic Signs:	Animals inspected twice daily; palpated for masses monthly
Survival:	Determined twice daily
Body Weight and Food Consumption:	Recorded weekly for 6 months and every month thereafter
Necropsy:	Performed on all animals; animals found moribund were killed. Gross and microscopic examination of all major tissues, organs and all gross lesions noted in killed animals as well as in animals found dead, when possible.
Hematology:	At 3, 6, 12, 18 and 25 months, the following parameters were evaluated on 5 rats/sex/dose: hemoglobin, hematocrit, RBC, WBC with differential and urinalysis.
Histopathology:	At 14 weeks and 112 weeks, 18 and 42 rats respectively were sacrificed and necropsied for gross and microscopic pathology.
Tissues Examined:	Liver, kidney, adrenals thyroid, lung, prostate gland, skin, spleen, stomach, lymph nodes (mesenteric), small intestine, large intestine, brain, uterus, mammary gland and ovary.

Results

Body Weights and Food Consumption: Suppression of body weight gain and food consumption in both males and females at 100 and 50 mg dose levels were observed. At 25 mg/kg, both males and females showed depression of body weight gain although the food consumption was normal. At 10 mg/kg, both sexes showed depression of body weight gain with normal food consumption.

Survival: At a dose of 100 mg/kg, 6 males and 4 females died after 6-7 weeks of treatment. After 12-13 weeks of treatment, 5 males and 4 females died at 50 mg/kg level whereas no deaths occurred at 25, 10 or 5 mg/kg during the first 3 months on test. The 25 mg/kg group was terminated at 65-73 weeks. The survival in % in the remaining groups was as follows: control - 92.8; 10 mg/kg - 92.8 and 5 mg/kg - 85.7.

Organ Weights: Seminal vesicle and prostate were smaller at 100 and 50 mg/kg dose levels than their respective controls.

Other Adverse Observations: Failure of secondary sex organ secretions, splenic hemosiderin, pulmonary edema and hemorrhage, inner adrenocortical atrophy, degeneration, hemorrhage at 100 and 50 mg/kg dose levels. In addition, thymic atrophy at 100 mg/kg level was observed. At 25 mg/kg level, adrenocoritical atrophy with fatty degeneration of the zona fasciculata and renomedullary fatty metamorphosis were apparent.

Hematology:

Hematology was performed on days 49, 90, 180, 360, 540 and 750 days of treatment. Lowering of hemoglobin and RBC values and neutropenia were observed after 7 weeks of treatment at 100 mg/kg dose level and at 50 mg/kg dose level.

Histopathology:

The incidence of hepatic benign nodular hyperplasia was as follows:

0 mg/kg	0%	(0/14);
5 mg/kg	36%	(5/14);
10 mg/kg	78%	(11/14);
25 mg/kg	71%	(10/14).

In addition, the incidence of hepatocellular carcinoma with lung metastases occurred in 21% (3/14) of the animals at 25 mg/kg level.

Comments:

No blood chemistry was performed either at the interim or at terminal sacrifices on any of the animals. The study is inadequate as a chronic study because the number of animals used were too few to assess the toxicity of the compound. However, due to the occurrence of hepatocellular carcinomas it is acceptable to assess its carcinogenicity.

Conclusions:

This study demonstrates that carbadox is a carcinogen as evidenced by the occurrence of hepatocellular carcinoma with pulmonary metastases in 21% of the females at the dose level of 25 mg/kg/day. A dose-related incidence of benign nodular hyperplasia of the liver in males and females was also observed.

3. A Two-year Chronic Toxicity Study of GS-6244 in Rats. Dose Levels of 2.5, 1.0 or 0 mg/kg/day

Report #/Date/Ref:	NADA 41-061 Vol. 9 6-10-70/data analyzed by Dr. S. H. Frazier
Petitioner:	Pfizer
Laboratory:	Pfizer
Test Substance:	Carbadox
Species/Strain:	Rat/Charles River crl:COBS(SD)BR
Duration:	742 days
Number/Sex/Group:	20
Dose Levels:	0(control), 1.0 and 2.5 mg/kg/day
Route of Administration:	In diet
Administration:	The test substance was mixed with the feed weekly. Symptomatology, body weight and food consumption were recorded weekly and drug levels adjusted accordingly.

Observations

Toxic Signs:	Animals inspected twice daily, palpated for masses monthly
Body Weight and Food Consumption:	Recorded weekly for 7 1/2 months and then every month thereafter.

Necropsy:	Performed on all animals; animals found moribund were killed. Gross and microscopic examinations of all major tissues, organs and all gross lesions noted in killed animals as well as in animals found dead when possible.
Hematology:	At 3, 6, 12, 18 and 24 months, the following parameters were evaluated on 5 rats/sex/dose: hemoglobin, hematocrit, RBC, WBC with differential, complete urinalysis and ophthalmoscopic examination.
Histopathology:	After 54 weeks and 106 weeks of treatment rats were necropsied for gross and microscopic pathology. At the dose level of 2.5 mg/kg, 7 males and 6 females, at 1.0 mg/kg dose level, 6 males and 5 females and at 0 mg/kg dose level 6 males and 5 females were examined for gross and microscopic pathology after 54 weeks of treatment. After 106 weeks of treatment, the distribution of rats for necropsy at the indicated dose levels was as follows: 2.5 mg/kg - 13 males and 14 females 1.0 mg/kg - 14 males and 15 females 0.0 mg/kg - 14 males and 15 females
Tissues Examined:	Brain, spinal cord, hypophysis, eye, submaxillary gland, thyroid gland, thymus, heart, aorta, lung, sternum, liver, spleen, pancreas, kidney, adrenal, stomach,

mesenteric lymph node, reproductive tract (male: testes, epididymides, seminal vesicle, prostate gland; female: ovaries, cervix and cornu of uterus), urinary bladder, femoral nerve, femoral bone marrow and mammary gland with skin.

Results

Body Weight and Food Consumption: Males receiving 2.5 mg/kg showed suppression of body weight gain at 58 weeks after treatment with the drug. However, the weights returned to normal at the end of the two year test period. Up to and inclusive of one year, all toxicological parameters were normal and no pathological changes attributable to the drug were observed among the rats that died or were sacrificed. The average weekly food consumption in gms/kg/day of male and female rats of the treated groups did not differ significantly from the controls.

Survival: At 54 weeks after treatment, 2 males and 1 female rat had died at 2.5 mg/kg dose level while no deaths occurred at 1.0 or 0.0 mg/kg dose levels. At termination (106 weeks), the survival was as follows:

0.0 mg/kg	37.5%
2.5 mg/kg	42.5%
1.0 mg/kg	45%.

Organ Weights: Significant decreases were observed between the controls and treated groups in both absolute or relative organ weights for brain, heart, kidneys, liver, spleen, testes, ovaries, thyroid and pancreas.

Histopathology: The incidence of benign nodular hyperplasia in liver was as follows:

0.0 mg/kg	10%
1.0 mg/kg	3%
2.5 mg/kg	26%.

A second type of lesion, which was drug related, termed peliosis hepatis (mottled liver) was observed in both males and females with the combined incidence as indicated:

0.0 mg/kg - 7%
1.0 mg/kg - 10%
2.5 mg/kg - 26%

Comments: A no-effect level could not be demonstrated in this study because several organ weights were adversely affected. No blood chemistry was performed either at interim or at terminal sacrifices on any of the animals.

Conclusions: This study corraborated the conclusions arrived at in an earlier study in which carbadox was administered in the diet at dose levels of 5, 10, 25, 50 and 100 mg/kg/day and found to be carcinogenic to rats. The present study has demonstrated that benign hepatic nodular hyperplasia does occur at a higher incidence in carbadox-treated (2.5 mg/kg) animals compared to controls. Such lesions may possibly be preneoplastic.

4. Brain Lesions in Rat Long-term Studies With GS-6244 (Supplemental to Report Submitted to the Agency February 19, 1970)

Report #/Date/Ref: DER 41-061 Vol. 1/Submission date April 25, 1973

Petitioner: Pfizer

Laboratory: Pfizer

Test Substance: Carbadox

Species/Strain: Rat/Charles River

Duration: 2 years

Number/Sex/Group: Study #1 - 56 animals
Study #2 - 85 animals

Route of Administration: In diet

Administration: Each compound was mixed with the feed weekly. The concentration of the compound in the meal was calculated based on the body weight and food consumption of the preceding week.

Results: The brain lesions originally reported as astrocytomas by dose level were reevaluated. The following is the incidence of brain lesions as originally reported as well as by current diagnosis:

Dose (mg/kg)	Age	Sex	Diagnosis	
			original	current
0	26 mo.	M	Medulloblastoma	Medulloblastoma
0	26 mo.	M	-	Inflammation
1.0	2 yr.	M	Astrocytoma	Inflammation
1.0	2 yr.	M	Astrocytoma	Microglioma (Mesenchymal)
10.0	24 mo.	F	Astrocytoma	Meningioma
10.0	24 mo.	F	Astrocytoma	Inflammation
10.0	26 mo.	F	Astrocytoma	Pituitary tumor
25.0	16 mo.	M	Astrocytoma	Mixed glioma

Conclusions:

There is no statistically significant evidence of a dose related effect of carbadox associated with incidence of brain tumors in rats. The results of trend analysis performed on each of the two studies indicated no significant trend.

Summary of Carcinogenicity Studies on Carbadox

A two year feeding study of carbadox and two different lots of desoxycarbadox was performed in rats using a single dose of 25 mg/kg bw/day for each compound. After 11 months of treatment, rats receiving both lots of desoxycarbadox showed multiple hepatocellular carcinomas throughout all lobes of the liver. All the rats receiving carbadox had nodular hyperplasia in the liver except two female rats which had hepatocellular carcinomas. No significant liver lesions appeared in the control rats at the termination of the study. The study is inadequate as a chronic study due to the small number of animals but is acceptable as a carcinogenicity study due to the occurrence of hepatocellur carcinomas in the treated animals.

A 26 month chronic toxicity study of carbadox was performed in rats using dose levels of 100, 50, 25, 10, 5 and 0 mg/kg bw/day. At the 100 mg/kg dose level, ten rats died after 6-7 weeks of treatment while approximately half of the 50 mg/kg group died after 12-13 weeks of treatment. The 25 mg/kg group was terminated after 65-73 weeks of treatment. A dose related incidence of hepatic benign nodular hyperplasia was observed in males and females. In addition, the incidence of hepatocellur carcinoma with lung metastases occurred in 21% of the animals at a dose level of 25 mg/kg. This study has demonstrated that carbadox produces malignant liver lesions in rats when administered in the diet. The study is inadequate as a chronic toxicity study but is acceptable as a carcinogenicity study.

A two year chronic study of carbadox in rats using doses of 0, 1.0 and 2.5 mg/kg bw/day indicated that hepatic nodular hyperplasia occurred at a higher incidence in carbadox-treated (2.5 mg/kg) animals than controls. A no-effect level was not demonstrated in this study because of the adverse effects on organ weights for brain, heart, kidneys, liver, spleen, testes, ovaries, thyroid and pancreas. The study is inadequate as a chronic toxicity study, however, it is acceptable as a carcinogenicity study because of the occurrence of nodular hyperplasia in carbadox-treated animals. These lesions may be regarded as preneoplastic.

A reevaluation of the brain lesions originally reported as astrocytomas in carbadox-treated rats was submitted by the petitioner. There was no statistically significant evidence of a dose-related effect of carbadox associated with incidence of brain tumors in rats.

III. Desoxycarbadox

A. Mutagenicity of Desoxycarbadox

Report/Date/Ref.	NADA 92-955 DER Vol. 3; review of Michael J. Prival dated February 14, 1977

Summary:

Desoxycarbadox gave a positive mutagenic response in Salmonella strains TA1535 and TA100 when activation was provided with rodent liver S-9. Liver obtained from rat, mouse and hamster all provide activity as measured in TA1535 with the rat being most active. Induction with Aroclor 1254 enhances the mutagenic response, while phenobarbital induced liver is not different from uninduced rat liver.

B. Carcinogenicity Study in Rats with Desoxycarbadox

Report/Date/Ref:	NADA 41-061, DER Vol. 5, pp. 1-255; review of August 15, 1978 of Dr. P. R. Sundaresan
Laboratory:	Pfizer Research Center, Amboise, France
Test Substance:	Desoxycarbadox, CP-17,056
Species/Strain:	Rat Charles River, CD (Sprague Dawley originated).
Duration:	Administration of compound was discontinued at day 350 at the highest dose and also for 50% of rats at the other 2 doses with all treatment subsequently discontinued at day 416. All survivors were autopsied at day 446.
Number/Sex/Group:	50/sex/dose level
Dose Level:	0 (Control), 5, 10 and 25 mg/kg/day

Route of Administration:	**Oral (in diet); during initial 3 months, the concentrations were adjusted at unspecified intervals according to body weights and monthly, therafter.**
Observations:	
Toxic Signs:	**Rats were observed for clinical symptoms once daily during the initial week and twice weekly thereafter.**
Survival:	**Cumulative mortality was plotted at 50 day intervals. Frequency of observation was not stated otherwise.**
Body Weight:	**Body weight was determined once weekly.**
Food Consumption:	**Was measured weekly during initial 3 months and once monthly thereafter and computed as g food/100 g body weight/day.**
Clinical Laboratory Analysis:	**The following hematology determinations were conducted at days 318, 413 and 447:** **Hemoglobin concentration, Red blood cell count, Hematocrit, Mean corpuscular hemoglobin,Mean corpuscular hemoglobin concentration, mean corpuscular volume, white blood cell count (WBC), and differential WBC.** **In addition, femoral bone marrow smears were taken from all animals autopsied at termination (day 447) and from moribund animals.**

Plasma was analyzed for the following constituents at days 318, 413 and at termination: glucose, urea, proteins, bilirubin, GOT, GPT, alkaline phosphatase, gamma-glutamyl-transpeptidase, sodium, postassium, and chloride.

The plasma was analyzed at the following intervals at day 318 at the high and medium dose levels for randomly selected animals with and without palpable abdominal nodules to give a total of 20 animals/sex. At the medium dose level (10 mg/kg), all animals with palpable nodules (10 females and 3 males) plus randomly selected "normal" animals to give a total of 20 animals/sex were used. At the low dose level (5 mg/kg), and in the control group, 20 animals/sex were randomly selected. At day 413, plasma was analyzed using 10 animals/sex/dose level (with or without drug withdrawal, respectively). At day 447, all surviving animals were used.

Necropsy: At termination, necropsy was conducted on all survivors. Individual body weights and weights of liver, kidney and testes were recorded.

The following tissues were processed for histological examination: Brain, kidney, heart, urinary bladder, bone marrow, ovary, pancreas, uterus, liver, mammary gland, pituitary, testis, thyroid, prostate, parathyroid, cervical lymph node, adrenal, mesenteric lymph node, lung, spleen and any other grossly observed tumor, and any lesion found in tissues not listed above including metastases.

Results:

Body Weights:

There was a drug-induced and dose-related growth delay which appeard from month 3 onwards and was more marked in females of the top dose level. From month 10 onwards, constant body weight losses were observed in rats of both sexes at the top dose level. This loss was not affected by drug withdrawal. At the low and medium dose levels, body weight losses appeared later.

Survival:

Survival rates at time of the final sacrifices were significantly lower at the high dose (both sexes) and at the medium dose levels (female). The percentage of survivors for males and females were as follows:

	Males	Females
Controls	96	94
5 mg/kg	92	90
10 mg/kg	90	74
25 mg/kg	26	40

The major causes of mortality in treated animals were drug-induced lesions including ulcerated or enlarged tumors, most of them in the mammary region, loss of weight and liver nodules.

Food Consumption:

The only observed difference was in the mean values (g/100 g body weight/day) on day 385 for females (8.0) compared to males (5.3).

Histopathology:

Histopathological changes

A dose-related increase was noted in the incidence of pigmentation of the renal tubules. This change, was more prevalent in females and associated with animals with liver tumors. Focal testicular degeneration was noted in some of the animals at the high dose and is considered due either to a toxic effect or to destruction of liver.

Tumors

1) Liver cell tumors (hepatocellular carcinomas and adenomas)

		Control	5 mg/kg	10 mg/kg	25 mg/kg
Heptocellular carcinomas	Before scheduled sacrifice	0	5	13	67
	At 15 months scheduled sacrifice	0	66	80	30
Adenomas		0	3	1	0
Total tumors		0/98	74/99	94/99	97/97

Spontaneous liver cell tumors are uncommon in these rats, and none were found in the controls in this study. The induced tumors were dose-related, and reached 100% in the top dosage group. Metastases were present in one animal at 5 mg/kg, 6 animals at 10 mg/kg and 31 animals at 25 mg/kg mainly in the lungs; of these metastases, only 3 were found in females.

2) Subcutaneous fibromas

	Control	5mg/kg	10 mg/kg	25 mg/kg
Before scheduled sacrifice	0	0	1	13
Sacrifice at 15 mos.	0	2	9	4
Total tumors	0/98	2/99	10/99	17/97

These tumors are rarely found occurring spontaneously in these rats. In this study, the response was dose-related , and all tumors occurred in males with the exception of 3 females, one in the 5 mg/kg group, and 2 in the top dosage group. In several instances, two tumors were present in the same animal.

3) Subcutaneous hemangiomas

	Control	5 mg/kg	10 mg/kg	25 mg/kg
Before scheduled sacrifice	0	0	1	25
Sacrifice at 15 mos.	0	0	4	18
Total tumors	0/98	0/99	4/99	43/97

These tumors rarely occur spontaneously in these rats. There was a dose-related response in this study with tumors occurring in both sexes. In many cases, these tumors were multiple, although this is not shown in the individual macroscopic observations.

When an animal has both malignant and bengin tumors at the same time, only the malignant tumor was counted.

4) Remaining tumors

No increase in incidence or decrease in latency of appearance was noted.

Organ Weights:

At each dose level and in each sex, both the absolute and the relative liver weights were highly significantly increased (P less than 0.001).

In the kidney and in the gonads, particularly at the top two dose levels, the absolute weights tended to be lower, while the relative weights were higher than their respective controls. The implication is that while there was a considerable fall in body weights (40% in the top dose males and 32% in the top dose females), the kidney and gonad weights also fall, but much less markedly.

Hematology Results

Two hematological changes were seen in rats receiving desoxycarbadox for 350 or 416 days at dose levels of 5, 10 and 25 mg/kg/day.

A moderate hypochromic microcytic anaemia at 25 mg/kg, and a slight anaemia at 10 mg/kg, in male and female groups.

Neutrophilia with a slight leucocytosis in the 25 mg/kg male and female groups.

In moribund animals, hyperplasia of the bone marrow was noted in about a quarter of the animals with anemia. At the final sacrifice, only a few bone marrow smears showed hyperplasia of the red cells.

Plasma Analysis Results:

A few dose related changes occurred in plasma enzymes, urea, bilirubin and glucose.

NEL: Not demonstrated due to the occurrence of hepatic tumors at all dose levels.

Conclusions:

The administration of desoxycarbadox to rats for 447 days was responsible for the induction of malignant tumors in the form of hepatocellular carcinomas, and benign tumors in the form of subcutaneous fibromas and hemangiomas. Mammary fibroadenomas were at least four times as numerous in all treated groups in comparison with the controls.

Hematological changes were seen in rats receiving desoxycarbadox for 350 or 416 days at dose levels of 5, 10 and 25 mg/kg/day including only a moderate hypochromic microcytic anemia at 25 mg/kg, and a slight anemia at 10 mg/kg, in male and female groups and neutrophilia with a slight leucocytosis in the 25 mg/kg male and female groups.

Desoxycarbadox administration resulted in dose and time dependent increases in plasma enzyme activities, urea and bilirubin. A dose-related hypoglycemia was observed in both sexes. Slight or no reversibility occurred after drug withdrawal. For other constituents, sporadic changes were encountered, but were not regarded as of biologic significance. Focal testicular degeneration was evident at the high dose level and was considered due either to a toxic effect or to destruction of liver.

Comments:

DT agrees with the previous review of Dr P. R. Sundaresan that desoxycarbadox is hepatocarcinogenic in rats when administered in the diet at doses 5, 10 and 25 mg/kg. This study is acceptable as a oncogenicity study but is not acceptable as a chronic toxicity study and cannot be used to support human safety.

V. Hydrazine

A. Determination

Hydrazine and hydrazine sulfate can be determined by titration, calorimetry and potentiometry (Feinsilver et al. 1959; Nair & Nair, 1971). Hydrazine can be quantitatively estimated using gas chromatography (Bighi and Saglietto, 1966) or spectrofluorometry (Vickers and Stuart, 1974).

B. Carcinogenicity studies in experimental animals

Rat: Severi and Biancifiori (1968) administered daily doses of 18 mg or 12 mg of hydrazine by stomach tube to 14 male and 18 female Cb/Se rats for 68 weeks. Lung tumors (adenomas and adenocarcinomas) were observed in 3/14 males and 5/18 females in 109 weeks. Out of 13 male and 13 female rats, hepatic cell carcinomas were observed in 4 male rats. No lung or liver tumors were detected in untreated controls (28 males and 22 females) surviving up to 104 weeks.

Mouse: Hydrazine given mainly as hydrazine sulfate produces a high incidence of multiple pulmonary adenomas and adenocarcinomas in different strains of mice. (Biancifiori & Severi, 1966). Lung tumors have been induced in Swiss mice (Roe et al. 1967; Toth, 1960, 1971), in CBA/Cb/Se mice (Biancifiori et al. 1963a; 1964; Biancifiori, 1969) and in BALB/C/Cb/Se mice etc. (Biancifiori, 1970a,b,c)

The incidence of pulmonary tumors produced by hydrazine sulfate was shown to be dose dependent in a study consisting of groups of 19 to 26 male and female BALB/C/Cb/Se mice. The lowest dose (21 mg) produced an incidence of 54% in males and 32% in females surviving up to 78 weeks. In control mice 24% of the males and 4% of the females developed pulmonary tumors, mostly between 90 and 100 weeks (Biancifiori, 1970a).

Hepatomas and hepatocarcinomas have also been observed in 3 strains of mice treated orally with Hydrazine sulfate (Biancifiori et al. 1964). However, Bhide et al. (1976) did not obtain any hepatomas in treated mice of Swiss, strong "A" and F_1 cross of ICRC (female) X C_3H (Jax) male as well as C17 male strains. Hydrazine sulfate acted as a carcinogen in all strains tested by Bhide et al. (1976) and lung tissue was the target tissue.

Hamster: No tumors were observed in Syrian golden hamsters after oral administration of hydrazine sulfate (Biancifiori, 1970d and Toth, 1972).

The "virtually safe" level for hydrazine sulfate was calculated as 11 ppb based on the net incidence of lung tumors (86%) in a mouse study at the dose level of 80 mg/kg/day (Biancifiori, J. Nat. Canc. Inst. 45, 965, 1970). The safe dose (S_m) for the meat was calculated using linear extrapolation and a risk of 10^{-6}. The current assay for hydrazine is inadequate to monitor the residues in the ppb range. Thus, the concern for human safety regarding the presence of hydrazine in the edible tissues of carbadox-treated pigs is warranted.

C. Other Relevant Biological Data

Absorption of hydrazine through the skin in dogs in rapid and the hydrazine can be detected in femoral blood in 30 seconds (Smith and Clark, 1972). Hydrazine is probably degraded to ammonia as evidenced by the elevation of blood ammonia in dogs given hydrazine; however, diacetylhydrazine is not degraded to ammonia (McKennis et al., 1959; Colvin, 1969).

Tissue Residue Studies on Carbadox and its Metabolites:

Since the Food Additive and Animal Drug Chemistry Evaluation Branch is preparing a detailed evaluation of metabolism and depletion studies on carbadox, only pertinent information in so far as it relates to the toxicology of carbadox will be dealt with here in this human safety reevaluation of carbadox. The following evaluation summarizes the areas of concern for human safety arising from deficiencies in metabolism and depletion studies:

1. The total residue depletion studies are inadequate by current standards. Pretreatment with cold carbadox was followed by a single radiolabeled dose. Thus, higher total residues than currently reported may be present.
2. The petitioner's total residue depletion studies were validated only at 100 ppb. Total residues 21 days post-medication were reported as 30 ppb but could be 100 ppb. The rate of depletion to lower levels beyond 21 days has not been reported by the petitioner.
3. No total residue depletion studies have been done to 1 ppb or less. A depletion study to this level may require a change in the target tissue and a marker substance other than quinoxaline 2-carboxylic acid (QCA).
4. Metabolites other than QCA exist at 7 days post-medication in the petitioner's radioactive residue depletion studies, and undoubtedly occur at later withdrawal intervals.
5. From the data submitted so far by the petitioner, the extent of comparison of the rat metabolism data and the swine metabolism data cannot be determined. In both areas, further information is required using a lower limit of detection for the metabolites.
6. From the petitioner's study of the methyl carbazate portion of carbadox, it cannot be determined how long this moiety and the hydrazine derived from it will remain in the animal following ingestion of carbadox.
7. Assays for quinoxaline 2-carboxylic acid (QCA) entail the use of an alkaline hydrolysis step. To what extent QCA is being generated from other carbadox metabolites in the analytical procedure is not known.

Details relevant to the metabolism and depletion of carbadox in swine can be found in DCH memo dated November 22, 1978, NADA 41-061. Based on this evaluation and in accordance with current standards, the DCH reviewer (Dr. T. S. Sulkowski) made the following observations and recommendations (DCH memorandum dated Dec. 11, 1978); see enclosed Attachment I).

1. Metabolism of Carbadox in Swine

The firm's metabolism studies in swine are inadequate by current standards. The firm should provide qualitative and quantitative information on the nature and number of carbadox related residues found in the four edible tissues of swine immediately post-cessation of drug treatment and at varying intervals thereafter. The individual metabolite levels should be detected and identified at levels obtainable by the best analytical technology available. The sensitivity of radiotracer methods should extend into the sub parts per billion range.

2. Metabolism of Carbadox in Toxicity Test Species

Data on the metabolism of carbadox in toxicity test species are very limited and do not meet our current standards. The firm should provide qualitative information on the nature of carbadox related residues in the tissues of each toxicity test species. Data generated in these studies should be obtained from test species while on medication and should employ tracer methodology.

3. Depletion of Total Residues, Selection of a Target Tissue, a Marker Residue, and Determination of the Assay Sensitivity.

In DT's memorandum of November 24, 1978 an S_0 of 0.68 ppb was stated to be the safe level for carbadox and its metabolites in the total daily diet. This equates to an S_m of 2 ppb in swine muscle and 6 ppb in liver. The S_0 of 0.68 ppb was obtained from the Mantel-Bryan extrapolation. Recalculation of the S_0 using the linear extrapolation approach will probably lead to a lower S_0 value and a concomitantly lower S_m.

Total residue depletion studies supplied by the firm did not proceed beyond 21 days post-treatment at which time total residues in liver were estimated by the firm to be less than 30 ppb. The swine in these studies were pulsed only once with radiolabeled carbadox following multiple dosing with unlabeled carbadox. The method of dosing is unacceptable by current measures and undoubtedly underestimates the total residues that would be found following adequate dosing with radiolabeled carbadox.

In view of the inadequacies of the previous depletion studies with carbadox and that the Sm for carbadox in the muscle of swine will be possibly in the sub ppb range, the firm should conduct a new total residue depletion study in swine. The depletion of the total residues in the four edible tissues should be followed to or below the levels dictated by the calculated S_o value.

The necessity of a total residue depletion study to the low or sub ppb range will require a selection of a target tissue, a marker residue and the determination of an assay sensitivity, R_m, required to monitor the total residues. The target tissue currently in use is liver -- with quinoxaline carboxylic acid (QCA) serving as a marker residue at an assay sensitivity of 30 ppb. Both the target tissue and the marker residue may be different at the low or sub ppb range. In any event, the current 30 ppb assay for QCA is inadequate to monitor either low or sub ppb residues of carbadox by any standard.

4. Regulatory Methodology

The firm must develop practicable, reliable and specific methods of analysis for the marker in the target tissue that are adequate for the enforcement of the acceptable level of risk for the residues of carbadox in swine tissue. The lowest limit of reliable measurement must be equal to or less than the R_m. These methods will include confirmatory procedures if the lack of specificity warrants their use. These methods must be validated within three government laboratories.

5. Practicable Pre-Slaughtered Withdrawal Periods

Using the regulatory determinative method, data must be provided from field use studies which will allow the assignment of practicable pre-slaughter withdrawal periods.

The above recommendation would have to be fulfilled in order to meet our current NADA requirements for the metabolism and depletion of carbadox in swine.

Discussion of the Safety of Carbadox and its Metabolites

Carcinogenicity and Mutagenicity of Carbadox and Desoxycarbadox

Carbadox and desoxycarbadox, one of its metabolites have been found to produce malignant liver cancers in laboratory rats. Hydrazine, a metabolite of carbadox is considered to be carcinogenic in rats and mice. The carcinogenic potential of other possible metabolites with the exception of quinoxaline 2-carboxylic acid is not known.

Carbadox is a carcinogen as evidenced by the occurrence of hepatocellular carcinoma with pulmonary metastases in 21% of the females at the dose level of 25 mg/kg and a dose related incidence of benign nodular hyperplasia of the liver in males and females. In this study, carbadox was fed in the diet at dose levels of 0, 5, 10, 25, 50 and 100 mg/kg/day. In another study in which carbadox was administered at 0, 1.0 and 2.5 mg/kg, benign nodular hyperplasia occurred at a higher incidence in carbadox treated (2.5 mg/kg) animals than controls. The association of benign nodular hyperplasia in the liver with drug treatment and concomitant occurrence of hepatocellular carcinomas was concluded by the Cancer Assessment Committee to be strong evidence for the carcinogenicity of carbadox. (Cancer Assessment Committee of the Bureau of Foods memorandum dated January 8, 1979 on 2-amino-5-nitrothiazole and carbadox; see enclosed Attachment II).

The safe level for the total daily diet of carbadox is calculated as 106 ppt based on combined male and female rat data on hepatic tumors with 99% confidence and a risk of 10^{-6} by the linear extrapolation method.

Carbadox has been shown to be mutagenic in a number of different assays. Increases in mutations were detected in both *Salmonella* strains TA 98 and TA 100 without activation. In addition, carbadox induced gene mutations in *E. coli* and *Klebsiella pneumoniae*, was positive in the *B. Subtilis* Rec-Assay (DNA repair), was positive in the mouse micronucleus test and caused increased chromosome aberrations in an *in vitro* mouse cytogenetics assay.

Desoxycarbadox is a potent hepatocarcinogen in rats when administered orally at levels of 5, 10 and 25 mg/kg body weight. In this study, the compound had to be withdrawn on day 350 from all animals at the top dose level and from 50% at the medium and low dose level groups because of high morbidity and mortality rates. At the top dose level, 100% of the animals had hepatocellular carcinomas, at the medium dose level 95% and the lower dose, 74%. Hepatic tumors were not observed in the control groups. In addition, desoxycarbadox induced benign tumors in other organs. The frequency was dose-related for skin tumors (fibromas and hemangiomas) but not for mammary gland fibroadenomas. Clinical chemistry examinations showed those modifications arising from severe liver disorder: increase in

GOT, GPT, AP, plasma and hepatic gamma-GT, increased bilirubin and reduced blood glucose. The Cancer Assessment Committee of the Bureau of Foods concluded desoxycarbadox to be a potent hepatocarcinogen in rats because of the high incidence of hepatocellular carcinomas in the rat (Cancer Assessment Committee of Bureau of Foods memo dated January 8, 1979; see enclosed Attachment II).

Desoxycarbadox was found to be mutagenic to Salmonella strains TA 1535 and TA 100 in the presence of S-9 derived from Aroclor-induced rat liver.

Extrapolation from the rat carcinogenicity data on desoxycarbadox to a "virtually safe" level in tissues establishes this value to be in the range of 200 ppt. The safe level (S_o) of desoxycarbadox for the total daily diet was calculated as 61 ppt based on combined male and female rat data on hepatic tumors with 99% confidence and a risk of 10^{-6} (one hit extrapolation). Current assays developed by the petitioner are unable to measure residues at this concentration. Carbadox is currently regulated by quinoxaline 2-carboxylic acid, its longest lived metabolite that has been identified. Chemical methods have determined this residue at 30 ppb at 21 days after the last treatment.

Carcinogenicity of Hydrazine

Carbadox is metabolized to quinoxaline derivatives and methyl carbazate (20% of the administered dose), the latter yielding on further degradation, carbon dioxide and hydrazine. Free hydrazine is present in pig urine to an extent of 7% of the administered dose after administration of side chain-labeled carbadox. It is also liberated after administration of labeled methyl carbazate in rats and mice since substantial amounts of $^{14}CO_2$ are exhaled in the breath.

Hydrazine is considered to be a carcinogen both in rats and mice. A high incidence of pulmonary tumors was observed in BALB/C/Cb/Se mice administered hydrazine mainly as hydrazine sulfate. The net incidence of lung tumors in a mouse study at the dose level of 80 mg/kg/day was 86% of the total number of mice administered hydrazine sulfate. The "virtually safe" level for hydrazine sulfate was calculated as 11 ppb using the linear extrapolation method. Thus the concern for human safety regarding the presence of hydrazine in the edible tissues of carbadox-treated swine is warranted.

Carcinogenicity of Quinoxaline 1,4-dioxide

Quinoxaline 1,4-dioxide has been demonstrated to produce nasal and liver tumors in rats when administered orally for 18 months at 10 mg/kg bw/day. There is a possibility that this compound may arise from metabolites of carbadox such as quinoxaline-N^1,N^4-dioxide carboxaldehyde and thus may produce nasal tumors. The occurrence of nasal tumors in the chronic feeding study of quinoxaline 2-carboxylic acid was not investigated. Thus this may be an area of concern for human safety. Of additional chronic/oncogenic studies are required on metabolites of carbadox, special attention should be paid to the histologic examination of nasal turbinates.

The strong concern for the carcinogenicity of carbadox and its metabolites creates the need to demonstrate more vigorously the absence of potentially carcinogenic residues. Present analytical methods are not capable of identifying the components of the residue. It should be pointed out that quinoxaline 2-carboxylic acid has been shown not to be a carcinogen both in experimental rats and mice. This would remove from concern for human safety only that portion of the residue which would be identified as quinoxaline 2-carboxylic acid. The petitioner would still have to demonstrate that the remaining residues in edible portions of the tissues are safe from the point of view of human safety.

Deficiencies in Subchronic, Chronic and Reproduction Studies

The petitioner has not submitted adequate subchronic studies to demonstrate a no-effect level for carbadox in the experimental animal. In a 30-day rat feeding study conducted at 50 and 100 mg/kg/day of carbadox in the diet and in a 60-day feeding study in swine at a dose level of 13.2 mg/kg/day of carbadox, a no-effect level was not demonstrated.

A 3-generation reproduction study on carbadox in rats also failed to produce a demonstrable no-effect level. In a second 3-generation reproduction study, only one level of carbadox (5 mg/kg/day) was tested and this dose caused a decrease in pup survival at weaning during the F_2 and F_3 generations. Reproduction studies in dogs and rats ("relay toxicity") using the tissues from swine fed 0, 20 and 200 ppm carbadox for 1 month were unacceptable since the quantity of drug-related residues in the swine meat was not determined. A 23-25 month chronic relay toxicity study in rats fed a diet in which livers from carbadox-treated swine was incorporated, was unacceptable because no residue determinations were made of rat tissues nor of the swine livers after carbadox treatment. In addition, the residue levels fed to animals in such a study would probably be too low to adequately assess the toxicity of the compound. In a similar manner, two relay toxicity studies in dogs fed meat from the carbadox treated pigs were found unacceptable.

Due to deficiencies with regard to the adequacy of histopathological examination and absence of a demonstrable no-effect level, a 7-week range finding study on quinoxaline 2-carboxylic acid was not acceptable. In addition, in a teratology study performed in rats, the female rats were not sacrificed prior to parturition and no examination of the effects of the drug on uterus, resorptions and prenatal effects was carried out. In anotner teratology study in rabbits, the petitioner did not submit the data on the skeletal and visceral findings on a litter basis, thus negating a definite conclusion regarding the acceptability of the study.

Deficiencies in Metabolism Studies

The petitioner's metabolism studies in swine are not adequate by current standards. The petitioner has not provided qualitative and quantitative information on the nature and number of carbadox-related residues found in the four edible tissues of swine immediately after cessation of drug treatment. The individual metabolites have not been detected and identified at levels that can be obtained by the best analytical methodology. The sensitivity of radiotracer methods has not extended into the subparts per billion range.

Data on the metabolism of carbadox in toxicity test species are very limited. The petitioner has not provided information on the nature of carbadox-related residues in the tissues of each toxicity test species.

The total residue depletion studies in swine were validated only at 100 ppb. The rate of depletion to lower levels beyond 21 days has not been reported by the petitioner. The swine in these studies were treated only once with radiolabeled carbadox following multiple dosing with unlabeled carbadox. This method of dosing may underestimate the total residues that would be present following dosing with radiolabeled carbadox.

The firm has not developed practicable reliable and specific methods of analysis for the marker in the target tissue that are adequate for the enforcement of the acceptable level of risk for the residues of carbadox in swine. The target tissue currently in use is liver with quinoxaline 2-carboxylic acid (QCA) serving as a marker residue at an assay sensitivity of 30 ppb. The 30 ppb assay for QCA is inadequate to monitor either low or sub ppb residues of carbadox by current standards.

Finally, additional data from field use studies using the regulatory determinative method, should be made available to the agency so as to enable the assignment of practicable pre-slaughter withdrawal periods.

Conclusions and Recommendations

The Division of Toxicology is of opinion that the human safety concerns regarding carbadox and its metabolites are sufficient to warrant a withdrawal action against carbadox because:

1. Carbadox and desoxycarbadox, one of its metabolites, have been found to produce malignant liver cancers in laboratory rats. Hydrazine, which is also a metabolite of carbadox, has been reported to produce malignant lung tumors in mice. The carcinogenic potential of other possible metabolites with the exception of quinoxaline 2-carboxylic acid, is not known. Quinoxaline 2-carboxylic acid is not carcinogenic in rats and mice. The safe levels for the total daily diet of carbadox and desoxycarbadox are 106 and 61 ppt respectively. The safe level of hydrazine for meat is 11 ppb.

2. Both carbadox and desoxycarbadox have been found to be mutagenic in a number of different assays. The likelihood that other metabolites of carbadox may be mutagenic and possibly carcinogenic is of concern to human safety.

3. The regulatory method of analysis for carbadox residues is based on an assay for quinoxaline 2-carboxylic acid which is considered as the longest lived metabolite. However, analysis of liver at 7 days showed that quinoxaline 2-carboxylic acid constitutes only 25% of the total residues with the remaining 75% unidentified. The analytical method for total radioactive residues has been validated to 100 ppb only. The sensitivity of the radiotracer method must extend to the subparts per billion range to establish depletion of the residue. Thus, current analytical methods are unsuitable for regulating the use of the compound or for demonstrating the depletion to safe levels following drug withdrawal.

If the Agency should decide not to take an action to withdraw carbadox, the Division of Toxicology suggests the following alternative course of action:

The first alternative would be to require the petitioner to develop additional information to assure that humans are not being exposed to residue levels of toxicological concern. In order to comply with this requirement, the petitioner would have to provide:

1. a total residue study with the sensitivity of the method extending to the lowest estimated safe level for carbadox and its carcinogenic metabolites;

2. metabolism studies in target (swine) and toxicity test (rat and mouse) species;

3. mutagenicity studies on residues of carbadox which have not been hitherto tested either for carcinogenicity or for mutagenicity;

4. regulatory analytical methodology to monitor residue levels of concern to human safety and
5. a withdrawal study employing the regulatory determinative method.

A second alternative would be based on the development and use of new consumption factors for edible tissues and selection of a new level of risk to be used in place of 10^{-6} in the estimation of the safe level of carbadox in the diet. However, the petitioner would have to provide a total residue study, a metabolism study in target and toxicity test species and a mutagenicity study as indicated under the first alternative.

(It has recently come to the attention of the Division of Toxicology, that new consumption factors for edible tissues are being developed by HFF-350 from the Market Research Corporation of America Menu Census IV (1972-73) consumption data and portion size data obtained from the 1965-66 USDA Nationwide Food Consumption Survey for individuals 25-44 years of age. It is DT's understanding that these consumption factors may be different from currently accepted values for edible tissues. Furthermore, the current practice of calculating "virtually safe" dose levels of animal drugs for a risk of one in a million may be subject to modification).

cc: HFF-150 (Blumenthal)
HFF-152 (Flamm)
HFF-154 (S. Lovre, T. Sulkowski, C. Swentzel, W. Greear, J. Stewart,
J. Hauswirth, R. Lorentzen, L. Valcovic, M. Arcos, L. Saslaw
R. Osterberg, R. Card)
HFF-350 (Scheuplein)

Mr. **Weiss**. What action has FDA taken in connection with this recommendation?

Dr. **Crawford**. It is among those compounds that we are reviewing, along with the dimetridazole and ipronidazole at the present time. As Mr. Dols mentioned, there is a method for carbadox. And the question before the agency and before the drug manufacturer is whether or not that method is sufficient or whether or not we can develop a better analytical method. So we are in the throes of yet another hard decision about another one of these compounds that you have correctly raised.

Mr. **Weiss**. You had indicated in your testimony that the United States is far more advanced than other nations in removing from the market unsafe drugs leaving residues in our food. But wasn't carbadox removed from the market in the United Kingdom because it is a carcinogen?

[A July 18, 1984, notice of withdrawal of carbadox from the market in the United Kingdom follows:]

CARBADOX: WITHDRAWAL DECISION (UNITED KINGDOM)

Following a review by an officially-designated Committee on Carcinogenicity of the UK Department of Health and Social Security five veterinary products containing carbadox have been voluntarily withdrawn from the market in the United Kingdom.[1]

The Committee reported its conclusions as follows:

(a) there is good evidence that carbadox is genotoxic;

(b) there is good evidence that carbadox and its first metabolite are carcinogenic in the rat;

(c) it is undesirable to administer genotoxic carcinogens to animals intended for use as food;

(d) evidence was considered which showed that no residues were detectable in pigs or pig-products following a four-week withdrawal period, but members were concerned that non-compliance with this withdrawal period would result in human exposure through a staple food to a genotoxic carcinogen;

(e) there was an unacceptable risk to both mill- and farm-workers exposed to carbadox during feed preparation and possibly a risk from carbadox metabolites in the urine of treated animals.

Dr. **Crawford**. Last year we received communication from the United Kingdom that carbadox was being delisted. The circumstances, as we understand them, are these. They had raised questions about the continued safety of carbadox and, I believe, had asked for some information about the possibility of more danger to feedmill workers.

The drug firm that marketed the product in that country decided that rather than go through those processes to withdraw the product from the market. So it has been delisted in the United Kingdom. We are unaware of similar actions in other countries, however.

Mr. **Weiss**. Injectable ivermectin, a drug used in horses, was withdrawn from the market in July 1984, 14 months after its approval. Agency files indicate that this drug presented "one of the

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[1] Notification from Ministry of Agriculture, Fisheries and Food, United Kingdom of 18 July 1984.

three or four most severe problems [CVM] has ever experienced and the most serious problem in horses involving an approved product that it has ever faced."

[A document entitled "Invermectin—Marketing Experience" containing this statement follows:]

IVERMECTIN - MARKETING EXPERIENCE

Merck and Company has submitted a NADA to provide for an injectable ivermectin product intended for OTC use in cattle. The product has not yet been approved and a decision regarding the propriety of OTC marketing needs to be made before the review can be concluded. The position currently held by BVM is that safe use of the proposed product requires Rx marketing at this time. This conclusion is based largely on reports of adverse reactions that have been received for the currently approved ivermectin injectable Rx product intended for use in horses.

It is important that those considering this issue understand, in general, the structure and purpose of our post approval drug monitoring system and how surveillance information is used in regulating animal drugs.

The heart of the system is the requirement that manufacturers of all approved new animal drugs submit to BVM reports of all adverse reactions which come to their attention. (21 CFR 510.300 provides for this reporting of adverse drug reactions.)

BVM also receives information directly by mail or "Hotline" telephone. This information is almost exclusively reported by veterinarians. Additional sources of information to supplement that voluntarily reported to the manufacturers and subsequently submitted to BVM are continually being sought after.

Information derived from marketing experience is needed because extensive testing by the manufacturer and careful review by FDA prior to approval do not preclude long term effects or conditions of use which may result in adverse reactions, once the drug is on the market. New animal drug applications are approved, even under the best of conditions, on partial information based on limited data and limited numbers of animals. Unexpected responses may occur in the field when an approved product is used on large numbers of animals and under varying conditions of use. There are no set formulas to follow in determining the point at which adverse reactions or misbrandings become serious enough to require withdrawal of a product from the market or other corrective action.

There may be valid reasons why data collected to support approval of an NADA may not be consistent with experience that develops after a product is released for commercial marketing.

1- The preclearance data may be based on a few hundred or a few thousand animals while commercial marketing may result in millions of animal exposures. Less common adverse effects may require this greater exposure to become apparent.

2- The number of weight classes, breeds, diets, locations, temperatures, etc. that are used in collecting pre-approval data are of necessity quite limited. Such limitations rarely occur in commercial marketing.

3- Preclearance trials are generally performed carefully by trained investigators under controlled conditions. The investigators are expected to be meticulous in following label directions as well as other instructions. Commercial distribution (at least OTC marketing) often results in administration of a drug product under extreme conditions by individuals of various levels of competence and training---both careful and careless, trained and untrained. The directions for use and margins of safety that appear to be completely adequate in the preclearance experience may be inadequate relative to the extremes in conditions and situations that occur once a product is marketed.

The above explains our need for, and dependence upon, post-approval surveillance to assist us in meeting our responsibilities to assure, insofar as possible, the safety and effectiveness of marketed drugs. It also explains, to some extent, the critical inconsistencies between preapproval data and post-approval experience that occurred with respect to Eqvalan (ivermectin). We have substantial concern that the same adverse effects may manifest themselves if and when the injectable ivermectin cattle product becomes commercially available.

BVM's caution regarding the active ingredient ivermectin derives largely from the fact that it is a new chemical entity and that the only experience we have had with it in actual use has been bad. For a seven month period (February 22, 1983 to September 26, 1983), BVM has received reports of 300 foreign and domestic adverse reactions following the administration of ivermectin in horses. One hundred and twenty-seven (127) of these reactions are from foreign sources. (The kinds of reactions described in the foreign reports are consistent with the U. S. experience.) Of the 173 U.S. reactions, one hundred and twenty-five (125) have been fully evaluated and forty-eight (48) have been partially evaluated. The U.S. information is summarized as follows:

U.S. Reactions to Ivermectin in Horses - Seven Months 2-22-83 to 9-26-83

Reaction	Non Serious	Serious Non-Fatal	Serious Fatal	Total
Injection Site[1]	21	21[3]	27	69
Anaphylactoid	0	0	8	8
No Detail in Report	0	0	9	9
Misc. Causes[2]	31	0	8	39
[Preliminarily Screened]	24	24	0	48
	76	45	52	173 (100%)

1. Includes involvement of head, neck, chest and legs.
2. Serious: colic, ruptured colon, clostridial toxemia. Non-Serious: Allergic, locomotion difficulties.
3. Skin slough, clostridia cultured, gas in tissues, head/neck 2X normal size, high fevers, neck swollen and sore with refusal to eat and drink.

From a regulatory standpoint, several actions have been taken. Following experience in Canada where the product was approved October 8, 1982, (4 months in advance of U.S. approval), the Canadian authorities required a Dear Doctor letter to be issued and label changes to be initiated. While the equine product was originally approved OTC in Canada, it is our understanding that the Canadian authorities have initiated proceedings to change the status of the equine product from OTC to Rx (an unusual procedure for them). Merck also proposed to send a Dear Doctor letter in the U.S. BVM reviewed and strengthened the proposed Dear Doctor Letter and it issued April 22, 1983. Merck revised the labeling in the U. S. to be consistent with the Dear Doctor letter. Subsequently, they submitted a supplement to their NADA to expand the indications for use of the product and formalize the previous labeling revisions. BVM refused to approve this supplement on September 15, 1983 partly on the grounds that the label warnings were not sufficient. Specific revised warnings were suggested to the firm. On October 11, 1983, not having heard from the firm on this issue, BVM sent a letter requiring additional warning information in the labeling. The letter made it clear that failure to revise the labeling would result in initiation of proceedings to withdraw Eqvalan from the market.

In BVM's opinion, the problem associated with Eqvalan is very serious. On a relative basis, it is one of the 3 or 4 most severe problems BVM has ever experienced, and the most serious problem in horses, involving an approved product that it has ever faced. Of the 2 or 3 other situations in a class with Eqvalan, the two most recent, Sansalid (348 deaths) and Vingard (98 deaths) bear interesting parallels to the case of Eqvalan. Each was the broadest spectrum anthelmintic then approved (for dogs) and for this reason both were extensively distributed and used immediately after approval. The preapproval data on both appeared to be adequate but failed completely to predict the actual marketing experience and both had to be removed from the market within 6 months after approval.

Those cases aside, Eqvalan has been responsible for the death of more horses in a shorter period of time than any product ever approved for that species, or to the best of our knowledge any product ever sold in this country indicated for use in horses. Prima Paste, an unapproved "probiotic", iron-containing supplement for horses was responsible for numerous deaths of 1-3 day old foals over the past year or so. FDA took immediate action against the product and it was recalled and is no longer being marketed. The Prima Paste situation was no worse than that which exists relative to Eqvalan.

While available information regarding adverse effects of unapproved products is meager when compared to that often available for approved products (because the requirement for submission to BVM of ADRs reported to the manufacturer applies only to approved products), information submission on approved products is far from perfect. Because the initial reporting of adverse reactions is voluntary and dependent upon the expertise of the observer, there is no basis for assuming that more than a very small percentage of the ADR's that actually occur are ever reported to BVM, even for approved products. Although it is more likely that serious, especially fatal, reactions will be reported than less serious reactions, even the majority of these serious reactions may go unreported. Therefore any attempt to calculate an "incidence rate" based on reported ADRs/quantity of product distributed is inherently misleading. Sales volume alone cannot mitigate the 52 deaths and 45 other serious ADRs associated with this product in its first 6 months on the market. Whether it appears equitable or not, from a practical standpoint, a product that has the potential to be administered to large numbers of animals in a very short period of time needs to be scrutinized with particular care to be certain that the initial decision to expose these large numbers is correct simply because the potential effect of an error may be disastrous.

It is important that BVM's deliberations regarding the cattle product be perceived relative to this experience with the equine product. Despite the firm's arguments that the two products are so dissimilar that no extrapolation is appropriate, they have failed to support this contention with any evidence presented to BVM up to this time except for potentially misleading "incidence rate" calculations based on foreign channels of distribution and foreign adverse reaction reporting systems (the effectiveness of which is undocumented) which are associated with products of unestablished formulation and unknown conditions of use.

The experience with the equine product has demonstrated the risk associated with attempting to predict the market experience of ivermectin products based upon pre-approval controlled studies and field trials. The principle basis for believing that a similar problem will not arise in cattle rests on suspect foreign marketing experience.

To decrease the potential for an undesirable post-approval marketing experience that is substantially different from the collected preclearance data, the cattle product must be given Rx status. Rx status is needed for this cattle product because under Rx marketing conditions label directions are more likely to be followed, and if adverse drug reactions do occur, they would be more likely to be reported and reported expeditiously.

Licensed practitioners would be generally more familiar with the continuing marketing experience for the approved equine product than would the laity. This familiarity would be expected to influence veterinarians to be more careful in observing label instructions when using the product themselves or when instructing cattle producers in proper use of the product. Rx status, in and of itself, implies that an increased level of care is needed to administer the product safely. The condition of animals to be treated, the equipment and methods used in administering the drug, and the provisions for post-administration surveillance and treatment can be expected to receive more careful consideration under conditions of Rx marketing.

If adverse or unexpected reactions do occur, the Bureau and the manufacturer are more likely to receive reports under Rx marketing. Veterinarians have become aware of our needs for such information through use of our publicized "Hotline," through our past distributions of annual summaries of adverse reactions which were distributed to over 15,000 veterinary practices and through BVM participation in educational efforts at veterinary institutions and professional meetings. Reports that originate from veterinarians are usually of higher quality, are more complete, and are submitted more quickly than from the laity and laypersons rarely submit information directly to the Bureau.

In light of the Eqvalan experience, it appears that we cannot in good concience approve the cattle product without the safeguards that Rx marketing provides. After a reasonable time interval and with appropriate warnings or other label revisions that experience or additional data demonstrate to be needed, the firm may petition, by submitting a supplemental NADA, for a change to OTC status. To permit OTC marketing of the cattle product at this time would clearly not be prudent.

Mr. **Weiss**. How many deaths were associated with the use of the drug in horses?

Dr. **Crawford**. In the horse, we would have to check to be exact, Mr. Chairman. My memory of it is that it was about 80 horses.

Mr. **Weiss**. Our information is that as of May 1984 there were 108. But if you would check the number and submit it for the record.

Dr. **Crawford**. We will update it.

[The information requested follows:]

As of July 31, 1984, 131 deaths were associated with the use of the drug in horses.

Mr. **Weiss**. FDA files also indicate that you had considerable difficulty getting the manufacturer to report serious adverse reactions to FDA within the 15-day time frame required by FDA's regulations. Some serious reactions apparently were not reported for more than a year. Was the information contained in these delayed reports used by FDA in determining that injectable ivermectin was no longer safe for use in horses?

Dr. **Crawford**. Actually, the reports that we received did come by and large from the manufacturer. We began to get earlier reports from sources other than the manufacturing company, and we inquired of them as to where were the reports. And I believe that they had difficulty, also, in receiving reports of deaths.

We wanted to know—as you know, no drug is completely safe. So it is expected that you will have a certain level of adverse reactions. We wanted to know what the level was; so we needed specifics. We needed to know, just as you have asked, how many horses were involved.

I think the firm had trouble getting the information and it represented sort of a community effort between us and them in order to get the exact figures.

In terms of the withdrawal of the product from the market—this is ivermectin for horses—it was voluntarily withdrawn by the drug company, not by FDA.

Mr. **Weiss**. Are you suggesting that the difficulty FDA had in getting the manufacturer to report serious adverse reactions associated with that drug within the 15-day time frame did not reflect a deliberate effort to create that difficulty, but resulted from difficulties the sponsor experienced in obtaining the information?

Dr. **Crawford**. This is our interpretation. We did make implications to the firm to report these things as fast as they could get them and, also, to survey the use of the product in the country and elsewhere to let us know what the situation was. I think they had some difficulty in getting it all together. So I do not think we could accuse them. The evidence we have would not allow me to accuse them of withholding the information.

Mr. **Weiss**. In a May 11, 1984, memorandum which we will insert into the record, Dr. R.A. Mason relied, in part, on reports of 72 serious reactions submitted by the sponsor in April 1984, in concluding that he did not consider ivermectin's continued approval worth the risk presented to the horse population.

[The memorandum follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Date · May 11, 1984

From R. A. Mason, HFV-214

Subject Eqvalan (Ivermectin) Injection for Horses, NADA 127-443

To Chief, Equine and Ruminant Branch, HFV-214

I have just completed an updated analysis of adverse reactions in U.S. horses to Eqvalan. The analysis includes information in the latest annual report (DER 127-443/Accession No. 125, 4/3/84) submitted by the firm. The period covered, therefore, is from the date of approval (2/22/84) to, and including the above annual report. A summary table of the analysis is attached. Some highlights from the table are as follows:

1. Reports involving 2066 horses have been received in the approximately 14 months since approval.
2. There have been 699 adverse reactions (ARs) reported in U.S. horses during the 14 month period.
3. There have been 321 "serious" ARs reported in U.S. horses in this time.
4. There have been 108 fatalities reported in U.S. horses in this time.
5. Six hundred thirteen of 699 ARs were "Probably Drug Related" as per HFV-210's algorithm.
6. Two hundred forty two of 321 "serious" ARs were related to injection site infections and/or swellings.
7. The evidence is mounting that injection site infections and fatalities can be expected even where good (aseptic) injection technique is used. The reports indicate at least 19 cases involving 8 fatalities and 4 Clostridial isolations where there is good reason to believe the injection site was adequately prepped, where a veterinarian did the injection, where the neck site was used, and where other infections can be ruled out as a cause of the infection.

In my opinion, the above facts indicate that Eqvalan (Ivermectin) Injection for Horses, NADA 127-443, is unsafe as marketed and labeled. I do not believe that the additional precautionary statements and adverse reactions section recently added to labeling will significantly reduce Eqvalan's potential to encourage injection site infections, neck/shoulder and leg inflammation, skin sloughs, Clostridial infections and toxemia and death. Such infections appear

~~appear~~ to be due to spore forming anaerobic Clostridial organisms against which alcohol, betadine, nolvasan, etc. skin swabbing will do little or no good. Additionally, the above changes in labeling will do nothing to reduce the incidence of fatal anaphylactoid reactions which accounted for nearly 18% of the fatalities associated with Eqvalan usage. The ~~incidence~~ number of ARs with this product has become ~~intolerable.~~ excessive

2 changes
RAM 5/10/84

In short, ~~[illegible]~~ I do not consider its continued approval worth the risk presented to the horse population. I would like to meet with you, and if you think it appropriate, Dr. Beaulieu, to discuss the possibility of withdrawal of approval of NADA 127-443.

Also, based on the 3-13 month delinquent reports in DER 127-443 (125), I am recommending an inspection assignment of Merck facilities to look for additional unreported ARs. The above meeting would seem an appropriate place to discuss this recommendation.

R. A. Mason, D.V.M.

cc: NADA, DER
HFV-210, SDRF
RAMason:pck(22):5/10/84

Mr. WEISS. I will also insert into the record a June 6, 1984, FDA letter to the firm, stating that, "most of these [72] reports * * * occurred in 1983, 3 to 13 months before the information was submitted to this agency."

[The letter referred to follows:]

JUN 6 1984

NADA 127-443

Merck Sharp and Dohme
Attention: Mr. R. R. Buck
Assistant Director
Regulatory Affairs
P. O. Box 2000
Rahway, New Jersey 07065

Gentlemen:

We refer to your annual drug experience report dated April 3, 1984 for Eqvalan (Ivermectin) Injection For Horses, NADA 127-443.

This submission contained reports of 72 serious adverse reactions involving the injectable ivermectin product approved for use in horses.

In addition, the submission reported 25 adverse reactions in dogs, 10 of which died following the administration of ivermectin. You should consider publicizing the fact that Eqvalan is approved for use in horses only and may be toxic and result in death when misused in dogs. We will continue to monitor this misuse and may disseminate the results of our analysis if similar information is not otherwise made available to practitioners.

All of the reports of adverse reactions in dogs occurred in 1983, three to fifteen months before the information was submitted. The ten (10) deaths in dogs associated with ivermectin use occurred 7 to 12 months before they were reported.

Most of the reports involving horses occurred in 1983, three to thirteen months before the information was submitted to this agency. The reports of adverse reactions in horses were not made within the 15-working days time-frame requested by this agency on April 20, 1983 when we met with you to discuss your pending "Dear Doctor" letter. At that time you agreed to the 15-day interval and we documented this request in our May 16, 1983 letter. We have operated under the 15-day rule since April 20, 1983 and Center personnel have discussed and referred to the 15-day period in numerous conversations with Merck representatives. At no time has Merck indicated they were not honoring the 15-day reporting agreement.

Based on an evaluation of the adverse reaction data in your recently submitted annual DER, together with other information submitted during the 14 months since approval of this product, we have concluded that Eqvalan (Ivermectin) Injection for Horses, NADA 127-443, is unsafe for use as formulated and labeled (See attachments 1 & 2). We do not feel that label changes and/or increased user awareness can reduce the numbers or severity of reactions occurring with Eqvalan to an acceptable level. The continued exposure of the horse population to a routine worming preparation like Eqvalan with its potential for Clostridial infection, toxemia and death cannot be justified. This is to advise you that we are recommending publication of an NOOH providing for the withdrawal of approval of NADA 127-443, and we request that you cease marketing Eqvalan at this time.

You may wish to avoid the administrative procedures associated with the above regulatory action by terminating marketing and voluntarily requesting withdrawal of NADA approval under the provisions of 21 CFR 514.115. We could permit this route of processing in spite of the outstanding safety issue since, in our judgement, such expedited handling would serve the public interest.

We expect to be informed of your intentions within 30 working days from date of receipt of this letter. Please address your correspondence to Dr. Andrew J. Beaulieu, Director, Division of Surveillance, HFV-210, Center for Veterinary Medicine, 5600 Fishers Lane, Rockville, Maryland 20857.

We will continue to expect all adverse reaction information for the approved Eqvalan product to be submitted within 15 working days as long as the application remains approved.

If you have any questions, do not hesitate to contact us.

Sincerely yours,

William B. Bixler, V.M.D.
Associate Director for Surveillance
and Compliance (Acting)
Center for Veterinary Medicine

cc:

NADA DER
SDRF, HFV-210(2)
HFV-200 HFV-214
HFV-100 HFV-230
HFR-2350

RAMason:ezb 5-8-84(8)

Mr. **Weiss**. Dr. Mason's May 11, 1984, memorandum also states: "[B]ased on 3- to 13-month delinquent reports * * *, I am recommending an inspection of Merck facilities to look for additional unreported [adverse reactions]." Did FDA conduct such an inspection, to your knowledge?

Dr. **Crawford**. I am not sure. Let me confer with my colleagues. I think—we will submit it for the record, but let me go from my memory. And that is, we called them in for a conference, pursuant to following through on the recommendation of Dr. Mason. And about the time we would have instituted such an inspection, there began to be communication about their voluntary withdrawal of the product. And I suspect that we did not conduct the investigation because of that; although I will have to check to be sure.

[The information requested follows:]

Yes, Dr. Mason recommended an inspection of Merck facilities, but it was decided in a subsequent meeting that his concerns would be handled by letter (attached) to Merck requesting cessation of marketing and voluntary withdrawal of the product.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville MD 20857

JUN 6 1984

Merck Sharp and Dohme
Attention: Mr. R. R. Buck
Assistant Director
Regulatory Affairs
P. O. Box 2000
Rahway, New Jersey 07065

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NADA 127-443
Page 2

Based on an evaluation of the adverse reaction data in your recently submitted annual DER, together with other information submitted during the 14 months since approval of this product, we have concluded that Eqvalan (Ivermectin) Injection for Horses, NADA 127-443, is unsafe for use as formulated and labeled (See attachments 1 & 2). We do not feel that label changes and/or increased user awareness can reduce the numbers or severity of reactions occurring with Eqvalan to an acceptable level. The continued exposure of the horse population to a routine worming preparation like Eqvalan with its potential for Clostridial infection, toxemia and death cannot be justified. This is to advise you that we are recommending publication of an NOOH providing for the withdrawal of approval of NADA 127-443, and we request that you cease marketing Eqvalan at this time.

You may wish to avoid the administrative procedures associated with the above regulatory action by terminating marketing and voluntarily requesting withdrawal of NADA approval under the provisions of 21 CFR 514.115. We could permit this route of processing in spite of the outstanding safety issue since, in our judgement, such expedited handling would serve the public interest.

We expect to be informed of your intentions within 30 working days from date of receipt of this letter. Please address your correspondence to Dr. Andrew J. Beaulieu, Director, Division of Surveillance, HFV-210, Center for Veterinary Medicine, 5600 Fishers Lane, Rockville, Maryland 20857.

We will continue to expect all adverse reaction information for the approved Eqvalan product to be submitted within 15 working days as long as the application remains approved.

If you have any questions, do not hesitate to contact us.

Sincerely yours,

William B. Bixler, V.M.D.
Associate Director for Surveillance
and Compliance (Acting)
Center for Veterinary Medicine

Mr. WEISS. According to a memorandum of a June 26, 1984, meeting, the company argued that it did not interpret the 15-day reporting requirement as imposing upon it the duty to submit the adverse reaction reports in question. It had, however, received those reports.

[The memorandum referred to follows:]

June 26, 1984

MEMO OF A MEETING

BETWEEN: Ken Davis
Mr. Nestle
Mr. Griffith of Merck

and

Andrew J. Beaulieu, DVM, CVM

SUBJECT: Ivermectin

Merck representatives expressed surprise at receiving our 6-6-84 letter requesting them to cease marketing Eqvalan and withdraw the NADA. They saw no increase in ADRs to support such a request and they noted an inconsistency in approval of a supplement on 4-11-84 and proposed withdrawal on 6-6-84. They thought the paste approval would improve the situation with the injection but were given no time to assess the impact of the paste approval. Canine ADRs were purportedly submitted in the first 6 months report and no response was received from CVM so they were surprised by the tone of our 6-6-84 letter on this issue.

Following this discussion, the firm informed Dr. Beaulieu that they will respond officially to our letter within a week or so to the effect that they have ceased marketing Eqvalan but do not propose a recall. They are concerned about the confidentiality of information in the NADA if it is withdrawn and will seek additional information on this issue before deciding whether to voluntarily withdraw the NADA.

Merck presented a written summation of the ADR information on Eqvalan (thru 6-20-84) which will be filed in the DER for review along with submitted publications regarding use of ivermectin in dogs.

Regarding the timeliness of submission of ADR reports for Eqvalan, the firm purportedly thought it was honoring the agreement reached in our April 20, 1983 meeting which they took to be expressed by our May 16, 1983 letter which emphasized submission within 15 days of the kind of ADRs "that prompted your Dear Doctor Letter." I explained this only addressed our particular concern that these reactions not be interpreted as "expected" due to the label statement regarding same and therefore they should be submitted in 15 days. Our understanding of the meeting on April 20, however, was that we wanted all information on ivermectin just as soon as we could get it. Merck said that there was apparently a misunderstanding on this point. Since we had tied the reporting on the cattle product to this previous understanding via our April 20, 1984 letter, the firm wished to clarify the situation.

Dr. Davis proposed that any serious or unexpected reactions including any involving Clostridial infections and/or death would be reported within 15 days, others would be reported semiannually or annually. Upon questioning, Dr. Davis agreed that it was no more trouble for the firm to submit all reports as soon as the information was compiled rather than batching them up for semi-annual or annual submission. I said the proposed 510.300 rewrite would permit submission of many reports within 30 rather than 15 days. Therefore Merck should make a conscientious attempt to report serious or unexpected reactions (especially fatalities) within 15 days and all others within 30 days (with the understanding that another week or so might be needed in special cases to accumulate complete reports, eg. lab analyses, etc.) Merck stated that this was acceptable to the firm.

AJBeaulieu

Andrew J. Beaulieu, DVM

cc:

NADA 127-443 DER
HFV-1
HFV-100
HFV-200
HFV-214(Scarr, Mason)
HFV-216
HFV-230

AJBeaulieu:ezb 6-27-84(10)

Mr. **Weiss**. In any event, would you search all your records relating to this particular matter, and submit them to us for the record?

Dr. **Crawford**. Mr. Chairman, we will submit all relevant documents on this issue for the record.

[The information requested follows:]

MERCK SHARP & DOHME RESEARCH LABORATORIES
DIVISION OF MERCK & CO. INC.
P. O. BOX 2000 RAHWAY NEW JERSEY 07065-0914

KENNETH G. DAVIS, DVM
DIRECTOR
REGULATORY AFFAIRS

December 5, 1984

Dr. Andrew J. Beaulieu, Director (HFV-210)
Division of Surveillance
Food and Drug Administration
Center for Veterinary Medicine
5600 Fishers Lane
Rockville, MD 20857

RE: NADA #134-314 EQVALAN
(ivermectin) Paste and
ZIMECTERIN Paste

Dear Dr. Beaulieu:

In response to your letter dated October 17, 1984, it is our intention to amend our labeling for subject product to include the following statement on the individual folding carton containing the dose syringe:

> "CAUTION: EQVALAN® Paste has been formulated specifically for use in horses ONLY. This product should not be used in other animal species as severe adverse reactions, including fatalities in dogs, may result."

This addition will be implemented under 21 CFR 514.(d)(1) and (e) at the next printing of labeling for EQVALAN® Paste.

Sincerely,

Kenneth G. Davis

Kenneth G. Davis, D.V.M.

KGD/dar

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

NADA 128-409

SEP 19 1984

Merck Sharp and Dohme Research Laboratories
Attn: Mr. Robert R. Buck
Assistant Director, Regulatory Affairs
P.O. Box 2000
Rahway, New Jersey 07065

Gentlemen:

We refer to your drug experience report dated July 19, 1984 for IVOMEC 1% Injection for Cattle, NADA 128-409.

The referenced submission consisted of seventy-eight complaints of adverse reactions associated with, but not necessarily due to, the use of IVOMEC in cattle, dogs, horses, pigs and sheep.

Sixty-five of the seventy-eight complaints are reported to have occurred in 1982 and 1983 (35 in 1982; 30 in 1983). Since your covering letter does not indicate that any of these were reported previously, it appears that considerable time elapsed before these reactions were reported to us. As stated in our letter of June 6, 1984 such delayed reporting is not in accord with the fifteen working days timeframe you agreed to on April [illegible], 1983 and recently reconfirmed by Dr. Davis in discussion with Dr. Scarr of this Center on September 12, 1984.

Once again we request that you submit all reports of reactions following the use of ivermectin, foreign and domestic, within fifteen working days.

Also, it will ~~help~~ greatly help expedite processing if each 1932 adverse reactions reporting form is completed to the fullest extent possible, including entry of the NADA number in box "7b." We thank you in advance for attention to this detail.

If you have any questions on these matter, please contact this office.

Sincerely yours,

David N. Scarr, D.V.M.
Acting Chief, Food Animal Branch
Division of Surveillance
Center for Veterinary Medicine

Page 1 of 4

NEW ANIMAL DRUG RECORDS AND REPORTS ABSTRACT	DATE September 13, 1984
☑ [illegible] ☐ [illegible] ☑ [illegible] ☐ OTC ☐ [illegible] REPORT ☑ SPECIAL ☐ 6 MONTH ☐ ANNUAL	NADA NO. 127-443 / [illegible] NO. 172
INFORMATION SUBMITTED Ltr From Firm ☐ CLINICAL & ANIMAL DATA ☐ COMPLAINTS ☐ MANUFACTURED ☐ LABELING ☐ QUANTITY DISTRIBUTED ☐ PROMOTIONAL MATERIAL ☐ STABILITY ☐ ADVERSE REACTIONS Complaint (s) ____ Animals Affected ____	MANUFACTURER Merck Sharp + Dohme DRUG Ivermectin TRADE NAME(S) Eqvalan Injection For Horses

REVIEWER: R.A. Mason, D.V.M., Ph.D. **Signature:** RG Mason 10/30/84

1. **REPORT PERIOD:** N.A. to ____
2. **CLINICAL DATA:** ☐ Submitted (See addendum) ☑ Not Submitted
3. **LABELING:** ☐ Submitted ☑ Not Submitted ☐ See Addendum

   The labeling listed below is in accord with that approved.

4. **PROMOTIONAL MATERIAL:** ☐ Submitted ☑ Not Submitted ☐ See Addendum

   The material listed below is consistent with the approved labeling & supporting data.

5. **QUANTITY MARKETED:** N.A. Units. A unit is equivalent to ____
6. **OTHER INFORMATION:** ☐ None ☐ Chemical/Stability data (See chemist's report)

   ☐ ADR (Review attached) ☑ See addendum

7. **ALERT:** ☑ No ☐ Yes (See addendum)
8. **ACTION:** ☑ No ☐ Yes [illegible]

ADDENDUM: This submission consists of a letter from Dr. Davis of Merck in reply to HFV-214's (Dr. [illegible]) letter dated August 1, 1984 regarding the discontinuation of marketing of this product.

The letter states that:

☑ cont'd on next page

PREVIOUS EDITION MAY BE USED.

Page 2 of 3

Sept 13, 1984	
127-443	ACCESSION NO. 172

1. Marketing and promotional efforts, including release and/or shipment of Eqvalan Injection under their control, ceased worldwide effective July 2, 1984.

2. The decision to discontinue marketing the product as currently constituted, is

3. Marketing will not be resumed without prior consultation with FDA.

4. They will destroy returned product and not permit its re-entry into marketing channels.

5. Merck does not plan a product recall since there was a three month back order for the product and they believe it is unlikely that inventory exists at the distributor level and very little is now held by the veterinarian.

6.

7. Merck does not, at this time, request withdrawal of approval of NADA 127-443 as the data in this NADA is referenced in NADA 134-314 for Eqvalan Paste and may be used in support of additional formulations for horses.

8. Merck will continue to submit periodic drug experience reports as required by 21 CFR 310.300.

☒ Cont'd on next pag

Page 3 of 3

DATE Sept. 13, 1984

FILE NO. 127-443

ACCESSION NO. 172

The letter closes by stating that the withdrawal of Eqvalan Injection from the market has not been well accepted by the veterinary profession and includes approx. a dozen copies of letters from veterinarians criticizing Merck's action.

☐ Cont'd on next page

NADA 128-409
Merck & Company, Inc.
Rahway, NJ
September 12, 1984

MEMORANDUM OF MEETING

PRESENT: Industry Representative

Dr. Ken Davis

and

CVM Representative

Dr. David N. Scarr

SUBJECT: IVOMEC (ivermectin) % Injection for Cattle

Dr. Ken Davis requested a meeting (unscheduled) when he was in the building on September 12, 1984, and I agreed.

Dr. Davis informed me that he was going to submit about 90 reports of adverse reaction that occurred in France following use of the product. He explained that the reports were old and not in accord with the time frames in our agreement, but that the firm had encountered problems in obtaining timely reports from some of their foreign offices. He said that he did not expect such extended delays to occur for future foreign reports since the requirements were made clear to the responsible personnel.

I stated that we recently received adverse reaction reports from Merck that also originated which were similarly delayed in France, and that Merck would receive a letter documenting our concern.

Dr. Davis thanked me for my time and again stated that he would expect that all future adverse reaction reports that occur following use of the product, both foreign and domestic, would be submitted in a timely fashion and in accord with our agreed upon time frames.

David N. Scarr, D.V.M.

MERCK SHARP & DOHME RESEARCH LABORATORIES
DIVISION OF MERCK & CO., INC.
P.O. BOX 2000 RAHWAY, NEW JERSEY 07065-0914

KENNETH G. DAVIS, DVM
DIRECTOR
REGULATORY AFFAIRS

July 11, 1984

Dr. David N. Scarr (HFV-214)
Branch Chief
Equine & Ruminant Animal Branch
Food and Drug Administration
Center for Veterinary Medicine
5600 Fishers Lane
Rockville, MD 20857

RE: NADA # 128-409; IVOMEC
Injection for Cattle

Dear Dr. Scarr:

Persuant to our discussions with Dr. Beaulieu to clarify the requirements for reporting adverse reactions, we wish to confirm, herein, the procedure which we believe was found mutually satisfactory:

1. Deaths and/or infections or suspected infections due to Clostridia will be reported within 15 working days following receipt.
2. Unexpected reactions or an increase in incidence of expected reactions will be reported within 15 working days following receipt.
3. All other reactions will be reported as soon as reports are completed and in any event within 30 to 60 days following receipt by our company. They will not be held for reporting at the time of our semi-annual or annual periodic reports as per current regulations.
4. The types of information requiring immediate reporting, as described in 21 CFR 510.300 (b)(1), will be reported immediately.

If your understanding of the procedure differs from our view, please let us hear from you.

Sincerely,

Kenneth G. Davis, D.V.M.

KGD/dar

cc: Dr. Andrew J. Beaulieu (HFV-210)

August 29, 1984

MEMORANDUM OF MEETING

BETWEEN: Drs. Gerald [illegible] Lang
Edward A. Boraski
Kenneth C. Davis
Representing: Merck Sharp and Dohme
Rahway, N. J.

and

Drs. David N. Scarr, HFV-216
Richard A. Mason, HFV-216

SUBJECT: Merck's Ivomec Injectable (Ivermectin) Surveillance System: NADA 128-409- For use in Beef Cattle and Female Dairy Cattle before Breeding Age (approx. 2 years of age).

Merck requested the meeting in advance. Dr. Davis explained that the purpose of the meeting was to bring CVM up to date on the adverse reaction situation for Ivomec in keeping with Merck's commitment prior to the approval of NADA 128-409.

Dr. Lang presented the firm's data on adverse reactions (AR's) in the United States for the period since approval on 2-13-84 through June, 1984. The information is as follows:

(1) Merck has established a designated telephone hot-line for the reporting of Ivomec AR's. The phone number has been made known to all of Merck's salespersons, nationwide, who in turn have made it known to veterinarians.

(2) From 2-13-84 to 6-30-84, there have been 24 U. S. complaints involving Ivomec (up to several dozen reactions occurred in some complaints).

(3) During the same interval were sold (based on 500# b.w./treatment). Merck estimates 80-85% of this amount of product has been used, or

(4) The 24 complaints were accounted for as:
14-frequent due to "other" causes (trauma, urea tox, bloat, etc.)
3-anaphylactoid (but with complicated histories)
2-fescue toxicities, Texas panhandle area
5-feedlot complaints where the attending veterinarian (3 different ones) incriminated Ivomec in cases of Clostridial infection but where outside diagnosticians were not permitted to examine the affected animals and where necropsies were not performed until 24 hours or more after death.

In summary, Merck feels that to date there have been no confirmed cases of clostridial infection caused by the drug following the injection of cattle with Ivomec.

Dr. Scarr complimented the firm on its system of surveillance for Ivomec reactions.

In response to some comments made by the Merck representatives, Dr. Scarr explained that the absence of contaminating bacteria in a bottle of the product itself did not necessarily exonerate the product in reactions involving infections of the injection site. We know that certain drug products, which themselves are not contaminated, may produce an anaerobic environment in surrounding tissues and potentiate the pathogenicity of certain chance bacterial invaders from the skin or possibly the circulation. In such cases, we have requested and obtained labeling revisions warning users of the possibility of such reactions and advising them of the importance of aseptic vaccination technique, post-vaccination observation and prompt treatment. In other words, while not contaminated with the causative organism, the product nevertheless may be a factor in causing the reaction and product labeling may need revision. Dr. Scarr indicated that the information presented suggested that there may be a need for enhanced warnings of the risk of bacterial infection. We will continue to monitor the adverse reactions before a final decision is made on this point.

There was a brief discussion of why different kinds of adverse reactions are being reported in Europe (primarily France) and in the United States (i.e., allergic reactions to the kill-off of Hypoderma spp. larvae in French cattle vs. the miscellaneous, tissue and alleged clostridial infections reported in United States cattle). The only explanations offered by the firm were the indemnities payed to French farmers who reported deaths related to grub kill-off and the fact that we have not yet experienced a Hypoderma larvae season in the U. S. since Ivomec was approved. [That time is now here! If we are going to see Hypoderma larvae allergic reactions in the U. S. this year, we should expect to see them in cattle treated in July through October].

The meeting ended with no unresolved issues. Merck made no requests of CVM; CVM made no recommendation necessitating a response by Merck.

Richard A. Maenn, DVM, Ph.D.

5/31/84

Page — of —

NEW ANIMAL DRUG RECORDS AND REPORTS ABSTRACT	DATE July 2, 1984	
☑ [illegible] ☐ [illegible] ☑ [illegible] ☐ OTC ☐ UPDATING REPORT ☑ SPECIAL ☐ 6 MONTH ☐ ANNUAL	NADA NO. 127-443	[illegible] 155
INFORMATION SUBMITTED LTR FROM FIRM ☐ CLINICAL & ANIMAL DATA ☐ COMPLAINTS ☐ MANUFACTURED ☐ LABELING ☐ QUANTITY DISTRIBUTED ☐ PROMOTIONAL MATERIAL ☐ STABILITY ☐ ADVERSE REACTIONS Complaint(s) ____ Animals Affected ____	MANUFACTURER Merck Sharp and Dohme DRUG Ivermectin TRADE NAME(S) Eqvalan Injection For Horses	

REVIEWER: R.A. Mason, D.V.M., Ph.D. Signature: RA Mason 7/10/84

1. **REPORT PERIOD:** Special to —
2. **CLINICAL DATA:** ☐ Submitted (See addendum) ☑ Not Submitted
3. **LABELING:** ☐ Submitted ☑ Not Submitted ☐ See Addendum

The labeling listed below is in accord with that approved.

4. **PROMOTIONAL MATERIAL:** ☐ Submitted ☑ Not Submitted ☐ See Addendum

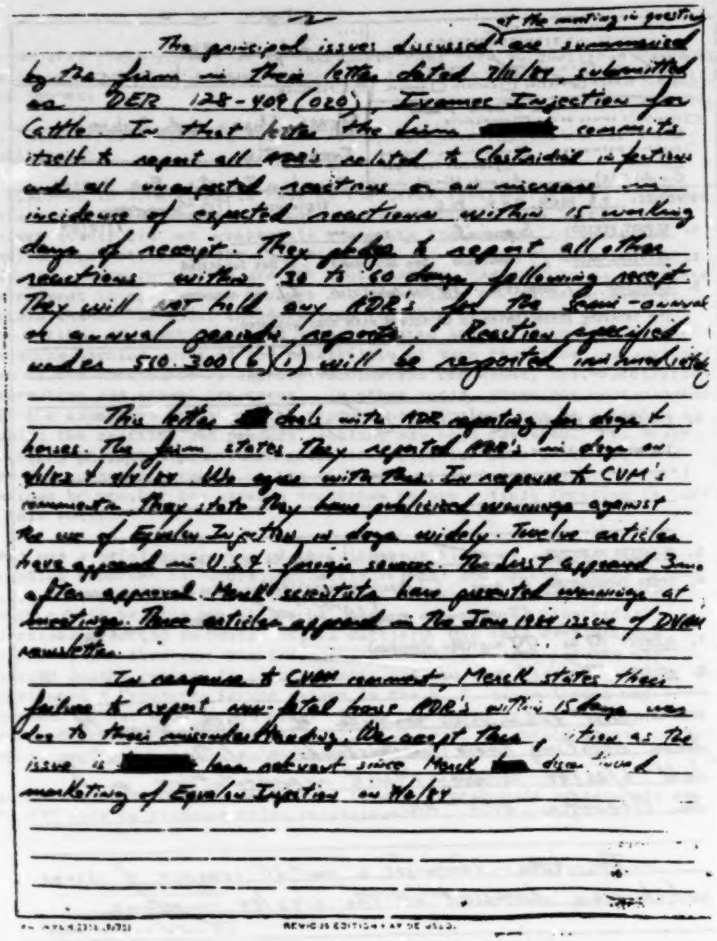
The material listed below is consistent with the approved labeling & supporting data.

5. **QUANTITY MARKETED:** — Units. A unit is equivalent to ____
6. **OTHER INFORMATION:** ☐ None ☐ Chemical/Stability Data (See chemist's report) ☐ ADR (Review attached) ☑ See addendum Jul 31 1984
7. **ALERT:** ☑ No ☒ Yes (See addendum)
8. **ACTION:** ☑ No ☐ Yes

ADDENDUM: This submission consists of a letter from the firm relating their understanding of the meeting held 6/26/84 between Merck representatives and Dr. Beaulieu, HFV-210.

This letter comprises a partial synopsis of issues which were discussed at the 6/26/84 meeting.

☑ cont'd on next page



-2-

The principal issues discussed at the meeting in question are summarized by the firm in their letter dated 7/11/84, submitted as DER 128-409 (020), Ivomec Injection for Cattle. In that letter the firm [redacted] commits itself to report all ADR's related to Clostridial infections and all unexpected reactions or an increase in incidence of expected reactions within 15 working days of receipt. They pledge to report all other reactions within 30 to 60 days following receipt. They will not hold any ADR's for the semi-annual or annual periodic reports. Reaction specified under 510.300(b)(1) will be reported immediately.

This letter [redacted] deals with ADR reporting for dogs & horses. The firm states they reported ADR's in dogs on 4/1/82 & 4/1/84. We agree with this. In response to CVM's comments they state they have publicized warnings against the use of Eqvalan Injection in dogs widely. Twelve articles have appeared in U.S. & foreign sources. The first appeared 3 mo. after approval. Merck scientists have presented warnings at meetings. Three articles appeared in the June 1984 issue of DVM newsletter.

In response to CVM comment, Merck states their failure to report non-fatal horse ADR's within 15 days was due to their misunderstanding. We accept their position as the issue is [redacted] been relevant since Merck [redacted] discontinued marketing of Eqvalan Injection in 4/6/84

PREVIOUS EDITION MAY BE USED.

Merck states "there have not been any changes in the reported incidence of adverse experiences in horses since Eqvalan Injection was first approved, including deaths from clostridial infections - - -."

Their letter states that

"based on the availability of the recently approved oral paste product which has the same efficacy but fewer side effects. [Although not part of this DER, Merck submitted a proposed press release dated 7/2/84 describing plans to discontinue marketing the injectable product. The press release was submitted under a cover letter to Dr. Crawford dated 7/2/84]. We will issue a letter to Merck in response to this action detailing further requested actions that are necessary to assure permanent removal of the product from the market. Also, our letter will describe how trade secrets can be protected in a withdrawn NADA. (This letter issued on or about 7/31/84).

(Happened 7/31/84)

Merck states that "- - at this time - - -" they are not requesting withdrawal of approval of NADA 127-443 nor do they plan a product recall. Our letter① relates to the first of these points. We will not request recall at this time. -END-

June 26, 1984

MEMO OF A MEETING

BETWEEN: Ken Davis
Mr. Nestle
Mr. Griffith of Merck

and

Andrew J. Beaulieu, DVM, CVM

SUBJECT: Ivermectin

Merck representatives expressed surprise at receiving our 6-6-84 letter requesting them to cease marketing Eqvalan and withdraw the NADA. They saw no increase in ADRs to support such a request and they noted an inconsistency in approval of a supplement on 4-11-84 and proposed withdrawal on 6-6-84. They thought the paste approval would improve the situation with the injection but were given no time to assess the impact of the paste approval. Canine ADRs were purportedly submitted in the first 6 months report and no response was received from CVM so they were surprised by the tone of our 6-6-84 letter on this issue.

Following this discussion, the firm informed Dr. Beaulieu that they will respond officially to our letter within a week or so to the effect that they have ceased marketing Eqvalan but do not propose a recall. They are concerned about the confidentiality of information in the NADA if it is withdrawn and will seek additional information on this issue before deciding whether to voluntarily withdraw the NADA.

Merck presented a written summation of the ADR information on Eqvalan (thru 6-20-84) which will be filed in the DER for review along with submitted publications regarding use of ivermectin in dogs.

Regarding the timeliness of submission of ADR reports for Eqvalan, the firm purportedly thought it was honoring the agreement reached in our April 20, 1983 meeting which they took to be expressed by our May 16, 1983 letter which emphasized submission within 15 days of the kind of ADRs "that prompted your Dear Doctor Letter." I explained this only addressed our particular concern that these reactions not be interpreted as "expected" due to the label statement regarding same and therefore they should be submitted in 15 days. Our understanding of the meeting on April 20, however, was that we wanted all information on ivermectin just as soon as we could get it. Merck said that there was apparently a misunderstanding on this point. Since we had tied the reporting on the cattle product to this previous understanding via our April 20, 1984 letter, the firm wished to clarify the situation.

Dr. Davis proposed that any serious or unexpected reactions including any involving Clostridial infections and/or death would be reported within 15 days, others would be reported semiannually or annually. Upon questioning, Dr. Davis agreed that it was no more trouble for the firm to submit all reports as soon as the information was compiled rather than batching them up for semi-annual or annual submission. I said the proposed 510.300 rewrite would permit submission of many reports within 30 rather than 15 days. Therefore Merck should make a conscientious attempt to report serious or unexpected reactions (especially fatalities) within 15 days and all others within 30 days (with the understanding that another week or so might be needed in special cases to accumulate complete reports, eg. lab analyses, etc.) Merck stated that this was acceptable to the firm.

Beaulieu

Andrew J. Beaulieu, DVM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville MD 20857

JUN 9 1984

NADA 127-443

Merck Sharp and Dohme
Attention: Mr. R. R. Buck
Assistant Director
Regulatory Affairs
P. O. Box 2000
Rahway, New Jersey 07065

Gentlemen:

We refer to your annual drug experience report dated April 3, 1984 for Eqvalan (Ivermectin) Injection For Horses, NADA 127-443.

This submission contained reports of 72 serious adverse reactions involving the injectable ivermectin product approved for use in horses.

In addition, the submission reported 25 adverse reactions in dogs, 10 of which died following the administration of ivermectin. You should consider publicizing the fact that Eqvalan is approved for use in horses only and may be toxic and result in death when misused in dogs. We will continue to monitor this misuse and may disseminate the results of our analysis if similar information is not otherwise made available to practitioners.

All of the reports of adverse reactions in dogs occurred in 1983, three to fifteen months before the information was submitted. The ten (10) deaths in dogs associated with ivermectin use occurred 7 to 12 months before they were reported.

Most of the reports involving horses occurred in 1983, three to thirteen months before the information was submitted to this agency. The reports of adverse reactions in horses were not made within the 15-working days time-frame requested by this agency on April 20, 1983 when we met with you to discuss your pending "Dear Doctor" letter. At that time you agreed to the 15-day interval and we documented this request in our May 16, 1983 letter. We have operated under the 15-day rule since April 20, 1983 and Center personnel have discussed and referred to the 15-day period in numerous conversations with Merck representatives. At no time has Merck indicated they were not honoring the 15-day reporting agreement.

Based on an evaluation of the adverse reaction data in your recently submitted annual DER, together with other information submitted during the 14 months since approval of this product, we have concluded that Eqvalan (Ivermectin) Injection for Horses, NADA 127-443, is unsafe for use as formulated and labeled (See attachments 1 & 2). We do not feel that label changes and/or increased user awareness can reduce the numbers or severity of reactions occurring with Eqvalan to an acceptable level. The continued exposure of the horse population to a routine worming preparation like Eqvalan with its potential for Clostridial infection, toxemia and death cannot be justified. This is to advise you that we are recommending publication of an NOOH providing for the withdrawal of approval of NADA 127-443, and we request that you cease marketing Eqvalan at this time.

You may wish to avoid the administrative procedures associated with the above regulatory action by terminating marketing and voluntarily requesting withdrawal of NADA approval under the provisions of 21 CFR 514.115. We could permit this route of processing in spite of the outstanding safety issue since, in our judgement, such expedited handling would serve the public interest.

We expect to be informed of your intentions within 30 working days from date of receipt of this letter. Please address your correspondence to Dr. Andrew J. Beaulieu, Director, Division of Surveillance, HFV-210, Center for Veterinary Medicine, 5600 Fishers Lane, Rockville, Maryland 20857.

We will continue to expect all adverse reaction information for the approved Eqvalan product to be submitted within 15 working days as long as the application remains approved.

If you have any questions, do not hesitate to contact us.

Sincerely yours,

William B. Bixler, V.M.D.
Associate Director for Surveillance
and Compliance (Acting)
Center for Veterinary Medicine

Firm's response dated 7/11/84 (copy attached) for NADA (128409) is a satisfactory response.
No follow-up necessary.
7/30/84

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville APR 30 1984

June 60 days

NADA 128-409

Merck Sharp and Dohme
Attn: Mr. Robert E. Bush
Assistant Director Regulatory Affairs
P. O. Box 2000
Rahway, New Jersey 07065

Gentlemen:

We refer to your drug experience report dated March 6, 1984 for Ivomec 1% Injection for Cattle, NADA 128-409.

The referenced submission reported fourteen separate incidents of death in cattle related to the use of Ivomec in France 3 1/2 to 4 1/2 months before this drug was approved for use in the United States on February 13, 1984.

It appears there was ample time for the reports to have been submitted to this agency before Ivomec was approved. We would like to know the reasons for the extended delay.

Also, we request that you submit information on cattle reactions to ivermectin in accord with the time frame established for Eqvalan Injection for Horses, i.e., within 15 working days. We understand that on March 30, 1984 Dr. Davis told Dr. Mason of our staff that he saw no problem in adhering to the same time frame used in reporting reactions in horses.

Please contact this office if you have any questions on this matter.

Sincerely yours,

David E. Scarr, DVM
Chief, Equine & Ruminant
Animal Branch
Division of Surveillance
Center for Veterinary Medicine

Page 1 of 2

NEW ANIMAL DRUG RECORDS AND REPORTS ABSTRACT	DATE April 2, 1984
TYPE ☑ NADA ☐ [illegible] ☑ [illegible] ☐ [illegible] ☐ [illegible] ☑ SPECIAL ☐ 6 MONTH ☐ ANNUAL	NADA NO. 127-443 — [illegible] 124
[illegible] LTR. FROM FIRM ☐ CLINICAL & ANIMAL DATA ☐ COMPLAINTS ☐ MANUFACTURING ☐ LABELING ☐ QUANTITY DISTRIBUTED ☐ PROMOTIONAL MATERIAL ☐ STABILITY ☐ ADVERSE REACTIONS Complaint(s) ——— Animals Affected ———	MANUFACTURER Merck Sharp & Dohme DRUG Ivermectin TRADE NAME Equalan Injection For Horses

REVIEWER: R.A. Mason, D.V.M., Ph.D. Signature:

1. REPORT PERIOD: Special to ——
2. CLINICAL DATA: ☐ Submitted (See addendum) ☑ Not Submitted
3. LABELING: ☐ Submitted ☑ Not Submitted ☐ See Addendum

The labeling listed below is in accord with that approved.

4. PROMOTIONAL MATERIAL: ☐ Submitted ☑ Not Submitted ☐ See Addendum

The material listed below is consistent with the approved labeling & supporting data.

David N. Scarr [illegible] MAY 2 1984

5. QUANTITY MARKETED: ——— Units. A unit is equivalent to
6. OTHER INFORMATION: ☑ None ☐ Chemical/Stability data (See chemist's report)
☐ ADR (Review attached) ☐ See addendum
7. ALERT: ☑ No ☐ Yes (See addendum)
8. ACTION: ☐ No ☑ Yes LTR. OF RESPONSE TO FIRM.

ADDENDUM: SOB. consists of firm's response to our (HFV-[illegible] & [illegible]) letter dated March 6, 1984 concerning "[illegible]" of [illegible].
In response to our 3 comments the firm states:

a. That the "mailgram" specifying a 24-36 hr. observation period post-injection was sent-out prior to the 12/12/83 meeting at which the 72 hr observation period was discussed. The firm will have all future labeling and advertising reflect the 72 hr period when the observation time is mentioned.

3. The firm agrees it may be confusing to state "Deaths from clostridia have been reported in some instances, resulting from failure to use sterile techniques for injection." They will revise the statement to [redacted] change the comma after "instances" to a period and will add a new sentence such as: "In some instances these deaths resulted from failure to use sterile technique for injection," in future printed matter. They do not agree that information submitted to us as ADE's has established that infection has followed the use of thorough aseptic technique.

March 30, 1984

MEMORANDUM OF TELEPHONE CONVERSATION

Between: Dr. Ken Davis
Merck Sharp & Dohme
(201)574-5957

and

Dr. Richard A. Mason
HFV-214

Subject: Adverse Reactions to Ivomec (ivermectin, Merck), 1% Injection for Cattle, NADA 128-409

At Dr. Scarr's direction, I called Dr. Davis to inquire whether he was aware of adverse reactions in cattle following the administration of the recently approved cattle product Ivomec. I specifically asked Dr. Davis if he was aware of adverse reactions to this drug that had occurred in Florida cattle.

Dr. Davis replied that he was aware of only three (3) ADR's to Ivomec throughout the U.S. and that to his knowledge these had not occurred in Florida.

The three cases consisted of one case of bloat and one neurological disorder (with tonic/clonic convulsions) which to them seems different than the usual neurologic signs seen with ivermectin toxicity in cattle. Dr. Davis could not recall the nature of the third ADR.

He said he would send use these reports very soon.

He said he saw no problem in adhering to the same time frame for reporting cattle ADRs that we had requested with the injectable ivermectin product for horses (Eqvalan, NADA 127-443).

Dr. Davis indicated there had been one case of a human ingesting 5 ml of the cattle product without serious consequences. They have a report from the attending physician and will also send this information to us.

We closed after I reminded Dr. Davis that we would expect the cattle reports soon and that he would soon be getting a letter requesting the same guidelines for reporting cattle ADR's that we had requested with horses.

R. A. Mason, DVM, PhD

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 15 1983

NADA 127-443

Merck Sharp and Dohme
Attn: Mr. R. R. Buck
Assistant Director
Regulatory Affairs
P. O. Box 2000
Rahway, New Jersey 07065

Dear Mr. Buck:

We wish to call your attention to the fact that we have not yet received the information on adverse reactions that occurred in horses treated with ivermectin, NADA 127-443, that you agreed to submit when we met with you on April 20, 1983.

As you recall, adverse reaction reporting was discussed during the above meeting which was held at your request in regard to your then pending "Dear Doctor" letter. At that meeting you agreed to promptly submit the information on eight reactions in horses in the United States as well as all the available information from Canada. You repeated your commitment when Dr Mason of our staff called you on April 28, 1983 and you said you hoped to submit the information in question on or shortly after the day of his telephone call.

A check of our records indicates this information has not yet been received. We request that you submit the information within 5 days or advise us immediately why you cannot comply with this request.

We also wish to formalize our request that adverse reactions of the kind that prompted your Dear Doctor letter be submitted within 15 working days rather than being accumulated for annual submission.

Sincerely yours,

David W. Scarr, DVM
Chief, Equine and Ruminant
Animal Branch
Division of Surveillance
Bureau of Veterinary Medicine

MERCK SHARP & DOHME RESEARCH LABORATORIES
DIVISION OF MERCK & CO., INC.
P. O. BOX 2000, RAHWAY, NEW JERSEY 07065

R. R. BUCK
ASSISTANT DIRECTOR
REGULATORY AFFAIRS

(201) 574-5057

May 3, 1983

Dr. Max Crandall (HFV-200)
Associate Director
Surveillance & Compliance
Bureau of Veterinary Medicine
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: EQVALAN (ivermectin)
Injection for Horses
NADA 127-443

Dear Doctor Crandall:

We are writing with respect to our new animal drug application for EQVALAN (ivermectin) Injection for Horses, NADA 127-443.

On April 20, 1983, I met with Drs. Guest, Crandall, Beaulieu, Scarr and Mason to discuss a letter which we proposed to send to veterinarians regarding the use of EQVALAN. The letter contained additional precautions on the use of the product. Several changes were recommended by the members of the Bureau. These changes were incorporated into a second proposal which was submitted for any further comment. Since there were no additional comments, the letter was printed and sent to veterinarians the week of April 26, 1983. Copies of the letter are attached for your information.

It was also requested at the conference that we compile and submit an up-to-date report of adverse reactions to the Office for Surveillance and Compliance.

An up-dated Adverse Reaction Report with the individual case histories is attached.

Very truly yours,

Robert R. Buck

RRB:daz
Attachments

cc: Dr. G. Guest - F & DA

MSDAGVET
Division of Merck & Co., Inc.
P.O. Box 2000 Rahway New Jersey 07065 U.S.A.

WILLIAM H. D. LEANING, B.V.Sc.
EXECUTIVE DIRECTOR, TECHNICAL SERVICES
ANIMAL HEALTH PRODUCTS

(201) 574-6763

April 22, 1983

ADDITIONAL PRECAUTIONS ON USE OF EQVALAN*

Dear Doctor:

There appear to be cases where the use directions and administration procedures in the EQVALAN Injection package insert have not been followed. When administering EQVALAN, proper site selection and careful aseptic technique are of the utmost importance.

As stated on the package insert, "Although very infrequent, death from clostridial infection can occur after intramuscular injection in the horse. If infection is suspected, appropriate antibiotic therapy should be initiated immediately". Because of the urgency of clostridial infections, penicillin given intravenously is indicated; if an intravenous formulation is not available, penicillin should be given intramuscularly in high dosage. Corticosteroids are contraindicated in the absence of rigorous antibiotic therapy. However, steroids, fluids and analgesics may be indicated as supportive therapy.

Remind the horseowner to observe the treated animals for 24 to 36 hours following injection and to immediately report any swelling or other sign of illness. If bacterial infection is suspected, initiate aggressive antibiotic therapy immediately.

In areas where a high risk of clostridial infection in livestock is recognized or suspected, simultaneous but separate injection of procaine penicillin with the EQVALAN is advocated as a precautionary measure.

Despite the need to emphasize the above precautions, our recent introduction of EQVALAN Injection has been a great success, and reports indicate the product is being widely used by veterinarians throughout the country. If you have questions, please call or write Dr. Robert F. Miller, Associate Director, Technical Affairs, at the above address, or phone (201) 574-5575.

Sincerely yours,

William H. D. Leaning

William H. D. Leaning, B.V. Sc.
Executive Director - Technical Services

* EQVALAN (ivermectin, MSD) is a registered trademark of Merck & Co., Inc., Rahway, New Jersey 07065

PROFESSIONAL GUIDELINES FOR THE USE OF EQVALAN* INJECTION FOR HORSES

DO	DO NOT
Give EQVALAN intramuscularly.	Do not give intravenously.
As illustrated in the package insert, use lateral neck muscles as the primary injection site, using aseptic technique.	The gluteal, pectoral or triceps muscles are not recommended injection sites.
Always use a separate sterile needle and syringe, preferably disposable, for each horse. A 20-gauge needle is appropriate for most horses.	Do not use the same needle on more than one horse.
Remind the horseowner to observe the treated animals for 24 to 36 hours following injection and to report any swelling or other sign of illness. If bacterial infection is suspected, initiate appropriate antibiotic therapy immediately.	Since bacterial infection may complicate tissue reactions, corticosteroids are contraindicated unless given as an adjunct to appropriate antibiotic therapy.

* EQVALAN (ivermectin, MSD) is a registered trademark of Merck & Co., Inc., Rahway, New Jersey 07065

MERCK & CO., Inc.
Rahway, New Jersey

May 3, 1983

EQVALAN
(ivermectin)
Injection for Horses

ADVERSE REACTION REPORTS
Domestic and International Markets

Attached are tables which summarize the EQVALAN Adverse Reaction Reports that have been received by Merck since those that were reported in letters from Dr. Kenneth G. Davis to Dr. Arthur W. Patterson dated April 13, 1982 and November 29, 1982.

Table 1 lists the adverse reactions reported in the U.S. Table 2 lists those that were reported from the International Market. Table 3 lists the doses sold and estimated doses used by country.

Following the Tables are the individual reports which have been recorded on Form FDA 1932 (3/81).

May 3, 1983

EQVALAN
(ivermectin)
Injection for Horses

Table 1

Reported Drug Reactions from the U.S. Market

(Dose: 200 mcg/kg of body weight, given IM)

No.	State	Problem(s)	No. animals that reacted*	Deaths
255	CA	Anaphylaxis/aneurysm (submitted 3/24/83)	1	1
256♦	FL	Sensitivity reaction	4	0
269	WY	Clostridial myositis	1	0
270	CA	Stiffness and swelling	1	0
278	IN	Unable to walk, swelling, temperature 103.4°F, and lateral recumbency. Possible clostridial infection.	2	1
280	IL	Clostridium septicum infection	3	1
282	NE	Hypersensitive, temperature 104.5°F, unable to turn in stall	2	0
283	NC	Swelling at injection site (8" x 10")	3	0
285	CO	Very swollen at injection site (vaccine also given), shock reaction. Animal was euthanized. Possible clostridial infection.	1	0
287	WA	Clostridium septicum infection	Unk.	1
289	NJ	Suspect anaphylactoid reaction	1	1
290	PA	Suspect anaphylactoid reaction	1	1

---

* Total reactions. Those animals which died in this grouping are repeated under "deaths."

♦ Experimental study--Ivermectin administered subcutaneously at 3X recommended dose.

May 3, 1983

EQVALAN
(ivermectin)
Injection for Horses

Table 2

Reported Drug Reactions from International Market

(Dose: 200 mcg/kg of body weight, given IM)

No.	Country	Problem(s)	No. animals that reacted*	Deaths
204	Uruguay	Clostridial infection	4	1
208	Uruguay	Allergic reaction	1	0
209	Uruguay	Skin papules, suspect allergic reaction	1	0
238	Brazil	Possible clostridial infection	7	5
242	Netherlands	Clostridial infection	1	1
248	Canada	Clostridial infection	2	1
254	Chile	Anaphylactic shock	1	1
274	So. Africa	Pain, muscle tremors	2	0
275	So. Africa	Sleepy, depressed, recumbent	14	0
286	Canada	Swelling at injection site; clostridial infection	14	8

---

* Total reactions. Those animals which died in this grouping are repeated under "deaths."

Mr. WEISS. Did FDA take any regulatory action in connection with the firm's apparent failure to meet agency reporting requirements?

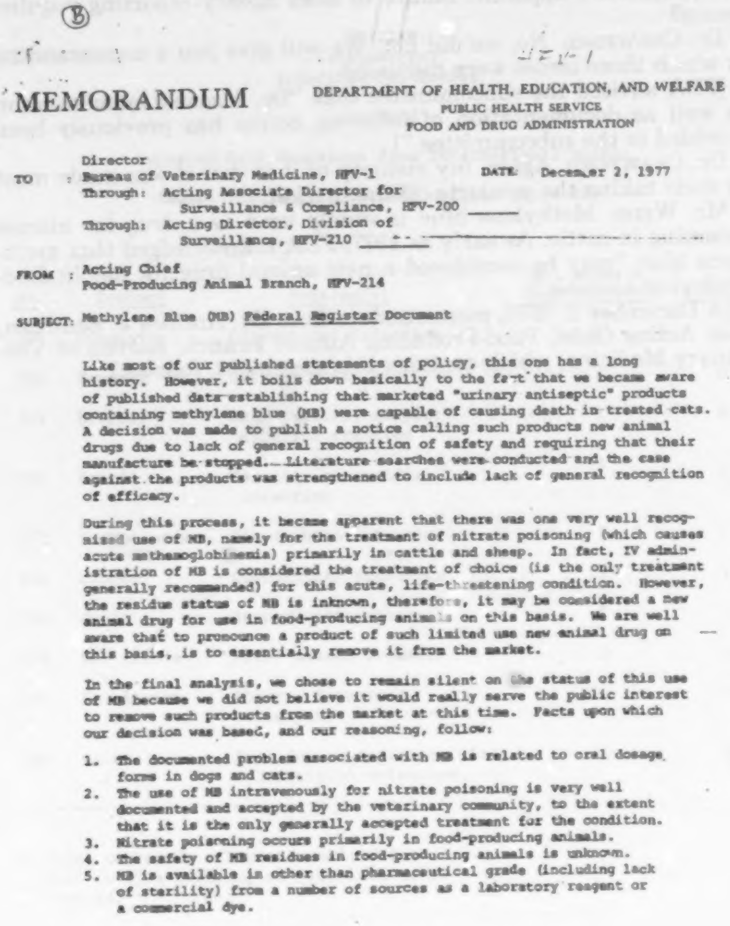
Dr. CRAWFORD. No, we did not. We will give you a memorandum in which those issues were discussed.

[FDA advised the subcommittee that "Dr. Mason's memorandum as well as documentation of followup action has previously been provided to the subcommittee."]

Dr. CRAWFORD. Again, my memory of it is that it was made moot by their taking the products off the market.

Mr. WEISS. Methylene blue is widely used as a drug for nitrate poisoning in cattle. As early as 1977, FDA acknowledged that methylene blue "may be considered a new animal drug for use in food-producing animals."

[A December 2, 1977, memorandum from Dr. Andrew J. Beaulieu, then Acting Chief, Food-Producing Animal Branch, Bureau of Veterinary Medicine, which contains this statement, follows:]



(B)

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Director
Bureau of Veterinary Medicine, HFV-1
Through: Acting Associate Director for
Surveillance & Compliance, HFV-200
Through: Acting Director, Division of
Surveillance, HFV-210

DATE: December 2, 1977

FROM : Acting Chief
Food-Producing Animal Branch, HFV-214

SUBJECT: Methylene Blue (MB) Federal Register Document

Like most of our published statements of policy, this one has a long history. However, it boils down basically to the fact that we became aware of published data establishing that marketed "urinary antiseptic" products containing methylene blue (MB) were capable of causing death in treated cats. A decision was made to publish a notice calling such products new animal drugs due to lack of general recognition of safety and requiring that their manufacture be stopped. Literature searches were conducted and the case against the products was strengthened to include lack of general recognition of efficacy.

During this process, it became apparent that there was one very well recognised use of MB, namely for the treatment of nitrate poisoning (which causes acute methemoglobinemia) primarily in cattle and sheep. In fact, IV administration of MB is considered the treatment of choice (is the only treatment generally recommended) for this acute, life-threatening condition. However, the residue status of MB is inknown, therefore, it may be considered a new animal drug for use in food-producing animals on this basis. We are well aware that to pronounce a product of such limited use new animal drug on this basis, is to essentially remove it from the market.

In the final analysis, we chose to remain silent on the status of this use of MB because we did not believe it would really serve the public interest to remove such products from the market at this time. Facts upon which our decision was based, and our reasoning, follow:

1. The documented problem associated with MB is related to oral dosage forms in dogs and cats.
2. The use of MB intravenously for nitrate poisoning is very well documented and accepted by the veterinary community, to the extent that it is the only generally accepted treatment for the condition.
3. Nitrate poisoning occurs primarily in food-producing animals.
4. The safety of MB residues in food-producing animals is unknown.
5. MB is available in other than pharmaceutical grade (including lack of sterility) from a number of sources as a laboratory reagent or a commercial dye.
)

6. Early toxicological work on MB was frequently confounded due to the presence of toxic impurities, particularly lead, in commercial preparations of methylene blue.
7. We are unable to publish a document at the present time which declares the general recognition of safety and efficacy of a product or class of products (i.e., and old drug monograph).

If we choose to announce that MB is a new animal drug for use in food-producing animals, we must determine whether interim marketing is to be permitted while data is generated. Based on past experience, we would permit interim marketing for this use but we are not prepared to permit interim marketing for the oral use in cats and dogs--a complication.

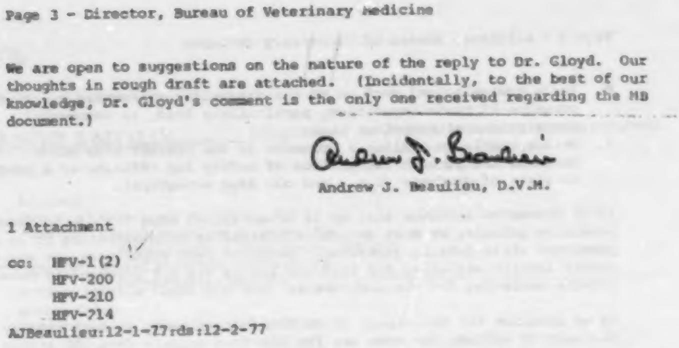
If we announce the NAD status of MB for food animals, we must clarify the document to exclude the same use for non-food animals from NAD status. In order to identify that class of products not subject to the NAD determination, we must identify them as old drugs, which we are prevented from doing. In any event, if we could do this, we would simply effect a relabeling of products to non-food animal use, knowing that the major use would still be in food-animals and any potential hazard to the consuming public would remain unchanged.

If we classified this use of MB as NAD in all species (a decision not likely to be supportable by expert testimony), then we would remove the sterile pharmaceutical products from the market, leaving the practicing veterinarian with the choice of letting animals die or using an inferior commercial grade of MB. On this basis, we feel sure that MB of inferior grade would be used and animals might suffer the consequences. Meanwhile, the potential hazard to consumers would not decrease and could increase due to impurities in the commercial preparations.

Based on the above considerations, we decided to specifically limit the document to the immediate problem involving death in dogs and cats due to oral preparations.

Unfortunately the AVMA in their concern that we not do what we have not proposed to do, may increase the significance of the situation to the point that we will have no option but to do that which neither the AVMA nor we want to do at this time.

Of course, if we become aware of any information to indicate that the continued use of MB in food-producing animals poses a threat to the public health, then we should move immediately to publicize the hazard and attempt to stop the use of all sources of MB regardless of the consequences to the animal population.



Page 3 - Director, Bureau of Veterinary Medicine

We are open to suggestions on the nature of the reply to Dr. Gloyd. Our thoughts in rough draft are attached. (Incidentally, to the best of our knowledge, Dr. Gloyd's comment is the only one received regarding the MB document.)

Andrew J. Beaulieu, D.V.M.

1 Attachment

cc: HFV-1(2)
HFV-200
HFV-210
HFV-214
AJBeaulieu:12-1-77rds:12-2-77

Mr. **Weiss**. Has methylene blue been approved for this use?

Dr. **Crawford**. No, it hasn't. It was approved at one time. As you correctly point out, it is an essential drug for dealing with animals and man that are poisoned with nitrates. It was approved at one time for use in small animals, dogs, and cats. There were difficulties with the effectiveness of it. It was approved for use in controlling certain urinary infections and urinary diseases. FDA had concluded by the late 1970's that it was no longer effective; therfore, it was withdrawn from the market and, therefore, was not marketed in a veterinary form. And for these occasional outbreaks of nitrate poisoning, there was no drug available to treat those diseases with.

Mr. **Weiss**. So you have a practical but not a legal basis for permitting the continued marketing of methylene blue for nitrate poisoning in cattle?

Dr. **Crawford**. As far as we know, it is available—as you probably know, Mr. Chairman—for use in human medicine where it is approved for use, and it is available through that form. And, also, it is available as a dye. So veterinarians and others, when nitrate poisoning outbreaks occur, sometimes obtain the dye in the pure form and prepare preparations in order to treat the animals. But it is not marketed as a veterinary drug at the present time.

Mr. **Weiss**. But in January 1979, you took the initiative to contact the Sigma Chemical Co., a manufacturer of methylene blue for nondrug purposes. You warned Sigma that it may not represent that the "chemical could be used for animal drug purposes," but also advised the company that FDA would permit it to sell the drug to veterinarians.

[Dr. Crawford's January 25, 1979, letter to Sigma Chemical Co. follows:]

Dr. Holt

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

Sigma Chemical Company
Attention: Mrs. Patricia Carr
P. O. Box 14508
St. Louis, Missouri 63178

Dear Mrs. Carr:

We have received a letter from the Oklahoma State University, College of Veterinary Medicine requesting assistance in expediting the purchase of the reagent methylene blue by veterinarians for use in their practices. To be of assistance in view of the forms your firm requires completed before shipping this chemical, we would like to advise you of our policy relating to such matters.

Reagents and other chemicals which are commonly used for non-drug purposes, such as methylene blue which is commonly used as a bacteriological stain and other chemical uses, may be sold to veterinarians without an obligation on your part to determine their intended use. You are not liable under the Federal Food, Drug and Cosmetic Act for the ultimate use or misuse of a chemical substance having common non-drug uses. Your firm would be subject to regulatory processes only if by written, verbal representation or other means indicated that the chemical could be used for animal drug purposes. This does not imply that you do not have a responsibility for chemical substances for which the only significant use is as a drug, e.g., sulfamethazine U.S.P. Your forms are appropriate for such chemical substances.

In summary, the Food and Drug Administration will permit methylene blue powder labeled for only chemical or laboratory uses to be sold to veterinarians without obligation on the part of the seller to predetermine the articles' intended use. We will be happy to assist you if you desire any additional information concerning this policy.

Sincerely yours,

Lester M. Crawford, D.V.M.
Director
Bureau of Veterinary Medicine

cc: T.R. Thedford, D.V.M.
Oklahoma State University
College of Veterinary Medicine

cc: HFV-1; HFV-230(2); HFV-236
HFA-224
Initialed: PSheeler; AHolt:1/24/79
EBallitch:km

Oklahoma State University

COLLEGE OF VETERINARY MEDICINE
Department of Medicine and Surgery

STILLWATER, OKLAHOMA 74074
(405) 624-6656 (Large Animal)
(405) 624-6731 (Small Animal)

January 11, 1979

Dr. Lester Crawford
Bureau of Veterinary Medicine
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Crawford:

This letter is to inform you about a problem we are facing at this time in Oklahoma concerning the availability of methylene blue. As you know this is the only known, effective antidote to Nitrate (Nitrite) toxicity in ruminants. As I understand the problem from talking to people in the pharmaceutical business and to Dr. Cheryl Knoblock in your division, methylene blue for use in dogs and cats was changed in status to a new animal drug. This classification necessitated new data be generated on the product or remove it from the market. Industry apparently felt it economically unfeasible to prove the product and found it unprofitable to continue marketing just the product used in ruminants for Nitrate toxicity. As a result, this product is no longer commercially available in a ready to use form.

I found a source of methylene blue powder from a chemical company but now discover that they are not allowed to sell this type chemical to anyone except research laboratories, etc., due to a F.D.A. regulation. At any rate they must have a statement that the substances they sell are not going to be used on food animals (enclosure).

To make a long and involved story somewhat shorter, here is our dilemma. We have just gone through one of the driest summers in years in this area. As a result of this we have very little grass left for winter use. Hay is expensive and in big demand. Much of the hay available for use is of the Sudan-Sorghum cross type and from tests run at the Oklahoma Animal Disease Diagnostic Laboratory and Oklahoma Forage testing laboratory, almost all of this hay is high in nitrate. Much of it is dangerously high.

As you can see our veterinarians are in a predicament as to how to treat the cases of nitrate poisoning we are experiencing. Obviously the producers are not happy with the situation either.

After visiting with Dr. Knoblock, I contacted Dr. Don Blevens of Bay-Vet in Kansas City, Missouri. Haver-lockheart, a subsidiary of Bay-Vet, is one of the companies who previously produced a methylene blue preparation for use against this toxin. He is checking to see if anything can be done to get the product back on the market.

This letter to you is to ask your assistance in expediting, in some fashion, the return of methylene blue to the availability of the veterinarian.

I feel this could best be done either by:

1. Encourage a commercial company to again prepare and offer for sale a standard solution of methylene blue, without undue expense or time consumption in proving efficiency and safety.

or

2. Some special release or permission for wholesale chemical companies to sell the powder to licensed veterinarians for compounding in their own offices.

It is necessary that this matter receive prompt attention. In the winter of 1977 - 1978, the Oklahoma Animal Disease Diagnostic Laboratory investigated over seventy cases involving cattle death attributed to nitrate toxicity. There were over 300 animals that died in these affected herds. This is estimated to represent only 5% of the losses suffered by cattlemen from this condition in this year. The conditions appear to be considerably more serious this year due to the draught conditions of the summer and fall. Without the availability of methylene blue I hesitate to consider what the potential death loss could be in the next sixty to ninety days.

I am eagerly awaiting your reply concerning this problem. Thank you for your prompt attention to it.

Sincerely,

T.R. Thedford

T. R. Thedford, D.V.M.
Extension Veterinarian

Enclosure:

c.c.

December 21, 1978

Haworth Veterinary Hospital
Box 2A
Chesterstar Route
Fairview, Okla. 73737

Attn: Dr. Mike Harworth

Gentlemen:

Since Government regulations make us responsible for what is in the mind of each customer when he places an order with us, we are trying hard to comply 100%. What you plan to use each reagent for, strongly affects the legal classification of that item and the regulations we must comply with. As unbelievable as this is, it seems to be the law.

Please carefully complete and return the enclosed questionnaire. A stamped, self-addressed envelope is enclosed also for your convenience. Your prompt cooperation will help prevent a delay in the shipment of orders to you.

Thank you for your cooperation.

Sincerely yours,
SIGMA CHEMICAL COMPANY

Patricia

PC/jr
Enclosures

Form PC72275

Mr. Weiss. Did methylene blue have any approved veterinary use at that time?

Dr. Crawford. No; it did not.

Mr. Weiss. In giving Sigma this advice, weren't you or FDA aware that it was likely that veterinarians receiving the chemical from the company would be using it to treat nitrate poisoning in cattle?

Dr. Crawford. Yes, we were; in fact, we so stated that was a possibility in emergency situations.

Mr. Weiss. In fact, in a July 22, 1980, letter to Sigma, Dr. Max L. Crandall, then CVM's Associate Director for Surveillance and Compliance, wrote: "We are aware that methylene blue is being used by veterinarians selectively for treating nitrate poisoning of cattle. * * * Although there is no approval for its use in animals, we will not object at this time to the sale of this chemical to practicing veterinarians for use only in their practice."

[The letter referred to follows:]

July 22, 1980.

Mr. Walter C. Stern,
Sigma Chemical Co., St. Louis, MO.

Dear Mr. Stern: This replies to your letter of June 13, 1980, regarding the marketing of methylene blue as a chemical agent.

Dr. Crawford's letter of January 25, 1979, was intended to address methylene blue specifically, rather than a general marketing philosophy for chemicals. Perhaps I can clarify the issue, because we concur with the general philosophy expressed in the first sentence of your letter. We believe chemical sales precautions are necessary and proper to avoid being party to or causing an illegal act.

Methylene blue presents a special situation. We are aware that methylene blue is being used by veterinarians selectively for treating nitrate poisoning of cattle. There is no other known antidotal treatment for this poisoning. Therefore, although there is no approval for its use in animals, we will not object at this time to the sale of this chemical to practicing veterinarians for use only in their practice.

We want to make a clear distinction, however, between this limited use and commercial marketing of methylene blue labeled or otherwise intended for drug use. Marketing methylene blue as a commercial drug is not permitted at this time. Furthermore, if we find that commercial drug products are being prepared from this chemical, we are prepared to immediately revoke our limited no objection position and invoke appropriate controls. Finally, we want you to know that this constitutes an informal advisory opinion which we may revoke at any time upon written notification to your firm.

Thank you for your concern in properly handling chemicals which may have drug uses. Please advise me if you need further clarification of our position.

Sincerely yours,

Max L. Crandall, D.V.M.,
Associate Director for Surveillance and Compliance,
Bureau of Veterinary Medicine.

Mr. Weiss. In a March 1979 animal drug memo, CVM even went so far as to tell veterinarians where to order methylene blue for their cattle practices.

[The document referred to follows:]

BUREAU OF VETERINARY MEDICINE

Animal Drug Memo

FDA

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service   Food and Drug Administration

Issued by: Industry Information Branch, Bureau of Veterinary Medicine
5600 Fishers Lane, Rockville, MD 20857 (301) 443-4557

A SUMMARY OF FDA ANIMAL DRUG ACTIONS AND RELATED ANNOUNCEMENTS PUBLISHED IN THE FEDERAL REGISTER February 1-15, 1979, AND OTHER ITEMS OF INTEREST

NEWS NOTES

Methylene Blue - A Problem And A Solution

Much of the Great Plains area--including Texas, Oklahoma, and Kansas--has been under varying degrees of drought this past year. As a result, large numbers of cattle herds have been affected with nitrate poisoning or methemoglobinemia, normally a sporadic seasonal problem. The drought has been so lengthy and extensive that summer pastures were affected, and much of the 1978 hay crop stored dangerously high levels of nitrates. Cattle have been dying from nitrate poisoning throughout the Great Plains area since last summer, and practitioners have discovered that metnylene blue, the one agent specific for treatment of methemoglobinemia, is no longer available commercially in ready-to-use form.

In March 1978, FDA published a final order in the Federal Register requiring approved New Animal Drug Applications (NADA's) for animal drugs containing methylene blue for oral administration to dogs and cats. The action was taken because of concerns arising over the safety and efficacy of such products to the treated animal. The new order was addressed only to oral dosage forms for use in dogs and cats. The American Veterinary Medical Association (AVMA) expressed formal concern about the need for emergency use of methylene blue for the treatment of ruminant nitrate poisoning. In response to a comment from AVMA, the Bureau of Veterinary Medicine informed the association by letter that the Federal Register final order pertained solely to the oral use of methylene blue in dogs and cats.

ADM-3-79

An FDA telephone survey of companies previously producing approved forms of both oral and injectable methylene blue labeled for use in animals revealed that the firms probably would not produce the substance again primarily because of economics and also because of staining problems in the production process.

An extension veterinarian in the drought-affected area tried to help his practitioner-readers by publishing in his newsletter a simple recipe for making injectable methylene blue from the chemical reagent powder. His story included the name, address, and phone number of a chemical company from which the powder could be purchased. However, practitioners experienced some difficulty when they placed orders for the chemical reagent because the company failed to understand FDA's regulations and policy with regard to the use of drugs and chemical substances by veterinarians in daily practice.

The extension veterinarian contacted the Bureau of Veterinary Medicine to learn what, if anything, could be done about the problem. After considerable discussion among Bureau personnel in a short period of time, the Bureau issued a letter notifying the company that a veterinarian is legally entitled to receive methylene blue (commonly used as a bacteriological stain) and other chemical substances with recognized non-drug uses to use in his practice as he sees fit. A firm may be subject to regulatory action under the Federal Food, Drug, and Cosmetic Act if the firm's written or verbal representations indicate that the chemical reagent could be used for animal drug purposes.

The policy of the Bureau of Veterinary Medicine continues to be that veterinary practitioners may use in private practice any drug or chemical which they can legally obtain, including human prescription legend drugs. There are two methods by which veterinary practitioners may obtain methylene blue. Veterinarians desiring to purchase chemical reagent methylene blue powder should contact chemical supply companies. If the companies express reluctance to ship such a chemical to a veterinarian, the company may contact the Case Guidance Branch (HFV-236), Bureau of Veterinary Medicine, 5600 Fishers Lane, Rockville, MD 20857 for information regarding the Bureau's policy in this matter.

Bulk drug-grade methylene blue powder is also available from another source. Two companies hold FDA approvals to sell human prescription, drug-grade methylene blue in 1-pound quantities: J.T. Baker Chemical Company, 222 Red School Lane, Phillipsburg, NJ 08865 (201-859-2151), $71.39/pound, will not sell directly to practitioners but will refer inquiries to a drug wholesaler in the area of the practitioner. City Chemical Corporation, 132 W. 22d Street, New York, NY 10011 (212-929-2723), $32.40/pound, will ship direct to practitioners upon receipt of a check including shipping charges.

Through providing this information to veterinary communicators, the Bureau hopes practitioners will be made aware of the availability of methylene blue.

Cheryl P. Knobloch, D.V.M.
Veterinary Communications Officer

FDA Withdraws Approval of Certain Dihydrostreptomycin Products

FDA has withdrawn approval of New Animal Drug Applications (NADA's) for "Dihydrostreptomycin Tablets with Carob Flour" (NADA 65-092), "Dihydrostreptomycin Bolus" (NADA 65-227), and "DHSM Sulfate Bolus with Vitamin A" (NADA 65-229).

These products contain dihydrostreptomycin with one or more of the following ingredients: kaolin, pectin, vitamin A, and carob flour for the treatment of calves for bacterial scours and swine for bacterial enteritis. The sponsor of the NADA's, Vet Products Co., Kansas City, MO, requested the [illegible]

Mr. **Weiss**. Doesn't this amount to fostering illegal use of an unapproved new animal drug?

Dr. **Crawford**. Well, it is a version of extra-label use. As you know, it is approved for use in human beings, including a level not to exceed 200 milligrams on a daily basis. It was not approved in veterinary medicine because there were no sponsors. The reason it was taken off the market in small animal medicine was because it was ineffective, according to the label claims. No one chose to market it for large animal use, that is, food animal use, because the market is so small. There are estimated to be only a dozen or so outbreaks in nitrate poisoning per year in the United States, and it is an orphan drug in the truest sense because no company could afford to market it. And, yet, there is essentially no other drug that is available that can be used to treat nitrate poisoning. So it was an extension of an extra-label use concept and it just essentially involved that kind of thing prior to the institution of the extra-label drug policy.

Mr. **Weiss**. In a December 2, 1977, memorandum, Dr. Beaulieu wrote: "Of course, if we become aware of any information to indicate that the continued use of [methylene blue] in food-producing animals poses a threat to the public health, then we should move immediately to publicize the hazard, and attempt to stop the use of all sources of MB regardless of the consequences to the animal population."

Is that still CVM's position?

[The memorandum referred to is in the record.]

Dr. **Crawford**. No. That is not the position. That was a 1977 memorandum. And I think there were—I was not here in 1977, but I suppose the position then was that we ought to evaluate all the possible hazards, including the hazard to human health, and make an appropriate move. After that time, it became apparent that there was nothing to treat infected cattle with, and the notion was that the hazard to humans would be very small, indeed, since there is such little use of it, and it is used only for nitrate poisoning. Then there is nothing else to treat these animals with in any case. So the policy of—that he evinced in 1977 was, in effect, changed by the Crandall Memorandum of 1979.

Mr. **Weiss**. Dr. Joseph Settepani of CVM wrote you last October, Dr. Crawford, that methylene blue has been shown to be a mutagen and should be considered "a highly suspect carcinogen."

[Dr. Settepani's October 22, 1984, memorandum to Dr. Crawford follows:]

OCT 2 2 1984

Director, Policy Development and Quality Control Staff, HFV-102

Methylene Blue

Lester M. Crawford, DVM, PhD
Director, Center for Veterinary Medicine, HFV-1
Through: Acting Associate Director for NADE, HFV-100

I am addressing this memorandum to you because a) it involves Center Policy and b) it proposes actions that, if undertaken, will involve every Associate Director's Office in the Center.

I was recently assigned the task of responding to a letter written to OADNADE by Dr. John Farnham in which he asks for our help in obtaining an approved NADA for the use of methylene blue for the treatment of nitrate toxicosis in ruminants. In obtaining background information for this response, I learned (Ref. 1) that methylene blue was reported to be mutagenic in a modified Ames test - an in vitro assay that exhibits a high correlation with the results of carcinogenicity testing in rodents. The recent conclusion by NCTR that gentian violet, which contains similar aromatic dimethyl amino groups, is a carcinogen in mice constitutes further evidence that methylene blue must be considered as a highly suspect carcinogen.

These facts raise some concern about the Center's continued encouragement of the use of this drug to treat methemoglobinemia that results when ruminants ingest high levels of nitrate.

As you know, methylene blue is not the subject of an approved new animal drug application. Nevertheless, CVM advised veterinarians of their right to use the compound as a drug in food-producing animals in a Drug Memo dated March, 1979 (copy attached) and, I understand, has reaffirmed this position many times since then. The advice is predicated upon the Center's extra-label drug use policy as it existed in 1979. It is unlikely that our current extra-label drug use policy would permit the use of a suspect carcinogen such as methylene blue in food-producing animals given the complete absence of any information in our files on the conditions of safe use of the drug.

In response to the facts outlined above, I propose the Center undertake the following actions:

1. Assign appropriate scientists to search the literature for information bearing on the safety, pharmacokinetics, methods of analysis and the usual conditions of drug use for methylene blue in animals.

2. Estimate a safe withdrawal period for food-producing animals treated with methylene blue based on the information found in number 1 above. Unfortunately, the March, 1979 memo does not mention the need to withold animals from slaughter for food following use of the drug.

3. Ask FSIS to institute an exploratory monitoring program using the most sensitive method for residues of the drug that we can find.

4. Assign a high priority to conducting research directed towards identifying another equally inexpensive drug that can replace methylene blue for treating methemoglobinemia resulting from nitrate poisoning.

The condition apparently arises when ingested nitrate is converted to nitrite in the GI tract of animals. Nitrite, in turn, oxidizes hemoglobin to methemoglobin, a derivative that cannot transport oxygen. Methylene blue (in its leuco or reduced form) effects a cure by reducing methemoglobin back to hemoglobin.

Given this mechanism, it should not be difficult to find a compound to replace methylene blue for this use. Dr. Weissinger provided another methemoglobin reducing agent acetylcysteine (Ref. 2), about two minutes after I described the problem to her.

5. Terminate the blanket authorization that the Center gave to Sigma Chemical Company in our Drug Memo and our letter of January 15, 1979 (copy attached) and institute case-by-case authorizations of sale of the drug. This procedure would enable the Center to contact individual veterinarians who receive methylene blue and advise them of the withdrawal period and of FSIS's monitoring program for residues.

6. Finally, explanation of the policy change with regard to methylene blue should be well publicized.

The proposals listed above represent my best shot at reaching an accommodation between the need for a drug to treat nitrate toxicosis when it occurs in food-producing animals and our mandate to insure a safe supply of animal-derived human food. There is no reason to believe that it cannot be improved upon by input from others within and outside the Center. I stand ready to help in anyway that I can.

(S)

Joseph A. Settepani, Ph.D.

References:

1. Chung, K-T, et al. "Mutagenicity Testing of Some Commonly Used Dyes", Applied and Environmental Microbiology, Vol. 42, No. 4, 641-648, 1981.

2. St. Omer, V.V. and E.D. McKnight III, "Acetylcysteine For Treatment of Acetaminophen Toxicosis in The Cat", J.A.V.M.A., 911-913, 1980.

Attachments - (4)

cc: HFV-2
HFV-100
HFV-101
HFV-344 (Weissinger)
HFV-200
HFV-400
HFV-500
R/D:HFV-102:JASettepani:jvp:10/22/84
F/T:jvp:10/22/84
#2408A

Mr. WEISS. Why hasn't CVM taken any action to terminate the unapproved use of the drug?

Dr. CRAWFORD. Well, we believe that the product is used in such limited circumstances and for such limited indications and only in animals that are virtually at death's door, that it poses little or no threat to the human population.

We also are cognizant of the fact that it is approved for use in human medicine with some warnings, to be sure, so we do not believe that it is conventional wisdom within the scientific community that this poses a threat to either man or animals. It is—according to the Settepani memorandum, there is the suspicion that it is a mutagen. And I think if there were to be another indication for use of the product we may have to reevaluate it. In other words, if it became widespread, that there became widespread usage in a variety of animal species intended for food, we would probably have to reevaluate our position.

Mr. WEISS. Dr. Crawford, Dr. Settepani stated that methylene blue has been shown to be a mutagen and should be considered a highly suspect carcinogen. He does not suspect it to be a mutagen. He says that it has been shown to be a mutagen.

But let me ask you about your discussion of its use as a human drug. You, yourself, pointed out earlier today that animal drugs can be much more dangerous than human drugs. Persons who eat animals containing residues of these drugs have no way of knowing that they are being exposed to these residues. In addition, the extent of exposure to these residues is not controlled. Just because an agent is approved for use as a human drug at specific doses does not mean that it is automatically permissible for use in animals. Isn't that correct?

Dr. CRAWFORD. I couldn't agree more.

Mr. WEISS. A November 28, 1972, FDA memorandum recommended that teat dips for the treatment of mastitis be characterized as a "new animal drug," a recommendation that has been reiterated several times since then.

[The memorandum referred to follows:]

Deputy Director, BVM, VM-2 November 28, 1972

Director, DVMR/BVM, VM-400

Statement of Policy at December 5th Meeting

This is in response to your memo of November 20, 1972, in which you request a proposed statement of what we think BVM policy regarding the use and handling of teat dips and sanitizers should be.

We believe the policy of BVM should be as follows:

> A product which is indicated solely as an aid in improving milk quality, such as an udder wash and/or teat dip (by means of reducing surface contaminants including bacteria pathogenic or not) is a food additive and requires an approved FAP.
>
> A teat dip or udder wash with direct or implied claims re mastitis should be categorized as a new animal drug, unless criteria are adopted by BVM for placing certain qualifying preparations in a " not new drug" category.

K. F. Johnson, D.V.M.

cc: Dr. Johnson, VM-400
Dr. Cazier, VM-400
Dr. Meyers, VM-430
DVMR, WM-400 -
CA-224
HMeyers/djp/11/28/72

READEX FICHE

Mr. **Weiss**. Does FDA require the marketing of teat dips to be supported by approved new animal drug applications?

Dr. **Crawford**. If I could back up a little bit on that, we have reviewed the possible regulation of teat dips for a number of years.

As you know, Mr. Chairman, these are solutions, for the most part, that are applied to the exterior of the cow prior to milking and are not animal drugs in the strictest sense.

Our concern about them down through the years is the theoretical possibility that these substances may somehow appear in the milk; that is, if the animal's udder is cleaned with them, there may be enough residue of the products to then appear in the milk. We have monitored that, and at one point we considered requiring an animal drug approval for each and every teat dip. We discussed that within the Center and actually had a number of meetings with concerned individuals about that.

We concluded that our level of concern was not high.

These types of products, for the most part, are regulated by other agencies, like EPA. We have—the toxicology of so-called organic iodine is well established, as is the toxicology of chlorine, which is contained in most of the other products that are marketed for this purpose. It is not an unknown area. It is an area of some concern.

Thus far, we believe it to be of insufficient concern to warrant registration of these products.

Mr. **Weiss**. Mr. Dols, do you know if the basic toxicology for the various unapproved teat dip products has been established by CVM?

Mr. **Dols**. No; that is not my field.

Mr. **Weiss**. Has CVM identified and studied the metabolites resulting from use of these various unapproved new animal drugs?

Dr. **Crawford**. No. No; we have not specifically, although the metabolites and other breakdown products, these chlorine compounds and also the organic iodine compounds, which are known by the term "iodoform," are well known.

Mr. **Weiss**. Are teat dip residues being monitored in the Nation's milk supply?

Dr. **Crawford**. We are monitoring for iodine in the milk. A level of concern is not sufficient to take the somewhat circuitous route of declaring teat dips an animal drug. We are concerned about the level of iodine that appears in the American milk supply and have regularly monitored for the presence of iodine.

Some teat dips do contain iodine; others contain chlorine and other products. So there is a suspicion that they may contribute to this iodine burden. There also is the more prevalent opinion that the iodine content of milk comes from the use of certain animal drugs that are added to the feed or added externally to the animal's body. One of these is a drug called EDDI, and we now have regulatory action pending against that product. We believe that is the great majority of the iodine problem, and we are dealing with it in that respect.

Mr. **Weiss**. Agency documents repeatedly express concern about the safety of residues left by teat dips in milk and the edible parts of food-producing animals. For example, notes added to an April 20, 1984, memorandum state: "We may be * * * compromising the public health by not holding some preclearance control that would occur from NADA approval."

[The memorandum referred to follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Date April 20, 1984

From Chief, Equine and Ruminant Animal Branch, DS (HFV-214)

Subject Teat Dip Products

To Deputy Associate Director for Human Food ~~Safety (HFV-300)~~
Through: Director, Division of Surveillance (HFV-210)

A meeting was held on 3/29/84 to discuss problems relating to continued marketing of new animal drug teat dip products for which we are currently not requiring formal preclearance approval prior to marketing. A copy of the memo of that meeting is attached.

As a follow-up to that meeting, we are requesting HFS to describe the kinds of data that would be required at this time to support human food safety for approvals of NADAs for the teat dips that are currently marketed. *

David M. Scarr, D.V.M.

cc: HFV-200, Dr. Bixler
HFV-210, Dr. Beaulieu
HFV-230, Mr. Bellitch
HFV-130, Dr. Gable
HFV-218, Dr. Meyers
HFV-236, Mr. Tassmer
HFV-133, Dr. Jacobs
HFV-210, SDRF
DMScarr:pck(3):4/20/84

* By a rigid position not to consider any deviation from guidelines, we are not protecting the public health... we may be, in fact, compromising the public health by not holding some preclearance control that would occur from NADA approval, and by not engaging the level of post marketing surveillance that would follow submission of DER's.

Mr. **Weiss**. Has the basic toxicology for the various unapproved teat dip products on the market been established by CVM?

Dr. **Crawford**. As I said earlier, we believe that level is probably not attributable to environmental causes and may result from the use of veterinary drugs which contain iodine and probably not, in the majority of cases, from teat dips. So we are taking action against those veterinary drugs that contain iodine and that could contribute to the iodine burden of the Nation's milk supply.

Mr. **Weiss**. Are you suggesting that the only teat dip residue that you would be concerned about is iodine?

Dr. **Crawford**. Iodine is a major one, Mr. Chairman, we believe. Chlorine also is contained in some of these products. It, likewise, is monitored for in milk. But, as you know, chlorinated water also is used to treat the milk lines with, and we do not see the level of increased chlorine that we do of iodine.

Mr. **Weiss**. Have methods been developed for detecting the various types of teat dip residues in milk and edible tissue for the purpose of monitoring for those residues?

Dr. **Crawford**. Actually, what we are monitoring for here is a sentinel element, which is iodine itself. And we believe if we monitor for it, then we will be—we will have a good fix on what the contamination of milk actually is.

Mr. **Weiss**. Have depletion studies been conducted on the various teat dip products being marketed for the purpose of determining a milk-withholding period or withdrawal period for slaughtering a treated animal?

Dr. **Crawford**. Depletion studies have been attempted on these veterinary drug compounds, which I mentioned earlier, like EDDI, which do contribute to the iodine burden. And they are—I think they are the state-of-the-art. For this reason, we are taking action against that class of products.

Mr. **Weiss**. FDA concluded in 1976 that there were questions about the safety and efficacy of medicated lick blocks for feeding and grazing animals and that, therefore, they are "new animal drugs" requiring premarket approval. Interim marketing of these unapproved drugs was permitted until the following year, however, to enable their manufacturers to obtain new animal drug approval. In 1980, FDA announced the third and final extension of the interim marketing deadline. Your current regulations state: "After February 22, 1982, all medicated blocks are required to have an application approved pursuant to Section 512 of the Act."

Are all medicated blocks now being sold covered by approved new animal drug applications?

Dr. **Crawford**. I cannot state that unequivocally. Some are and some are in the process of obtaining approval. We also occasionally become aware through FDA field staff of some that are being marketed without an approval or without the attempt to get an approval. And we have recently and on a continuing basis taken regulatory action against companies seeking to do that.

Mr. **Weiss**. What action has FDA taken in——

Dr. **Crawford**. The most recent case involved an inspection of the firm's facilities and the determination that they did not have nor were they seeking an approved application for these products. So they were sent a letter, which we call a notice of adverse findings, indicating that they can no longer market it, and that we would be monitoring the firm and that they must cease marketing as of that moment.

Mr. **Weiss**. When was that done?

Dr. **Crawford**. That was done last month. And I should say, Mr. Chairman, that there were a number of instances down through the years where we have had to do that.

Mr. **Weiss**. Would you submit for the record copies of those——

Dr. **Crawford**. Yes; we will.

[The information requested follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 13 1985

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. James H. Kent
President
Kent Feeds, Inc.
1600 Oregon Street
P. O. Box 749
Muscatine, Iowa 52761

NOTICE OF ADVERSE FINDINGS

Dear Mr. Kent:

Our Kansas City District Office recently (March 5/7, 1985) inspected studies conducted by your firm and Mr. Art Dean, Ada, Oklahoma; Mr. Harry Lehenbaur, Kingdom City, Missouri; Mr. Andy Ingram, Strafford, Missouri, and Dr. Glen A. Mente, Senior Vice President of Nutrition and Product Development, Kent Feeds, Inc., Muscatine, Iowa, utilizing the drug Lasalocid (Hoffman-LaRoche, Inc.) in a self-fed medicated block under INAD 2422.

This inspection revealed serious deviations from the intent and provisions of the new animal drug requirements of the law and regulations (Section 512 of the Federal Food, Drug, and Cosmetic Act and Title 21, Section 511.1(b) of the Code of Federal Regulations) as follows:

1. Your firm and the associated firm of C.K. Processing Co., Muscatine, Iowa, have produced, shipped, or caused to be shipped, and performed field trials on a medicated block containing a new animal drug (Lasalocid) without the required approvals. An Investigational New Animal Drug Application is required for testing such a new dosage form.

2. The medicated blocks were shipped in interstate commerce without the required investigational drug labeling, including the required investigational drug caution statement.

3. You have disposed of the remaining investigational drug product in an unapproved manner, in that the blocks were reportedly fed to confined cattle intended for slaughter, which were not subjects of a controlled clinical trial and for which there are no approved label directions for use, withdrawal periods, etc.

4. You utilized a greater number of animals for clinical trials than the numbers supplied on the Notice of Claimed Investigational Exemptions for Shipment of a New Animal Drug, which were submitted to the agency by Hoffman-LaRoche.

5. Further, we wish to point out to you that under 21 CFR 558.311 for Lasalocid, there is no approved regulation for medicated blocks, and therefore, the regulations require that you obtain your own INAD in order to pursue investigational studies intended to support a marketing application (New Animal Drug Application-NADA) for your (Kent Feeds) ENERGIBLOCK medicated blocks. Under the regulations, Hoffman-LaRoche, the manufacturer of the approved Bovatec premix (Lasalocid), is not permitted to transfer sponsorship of their original INAD #2422 to your firm for development of your product. Thus, INAD #2422 does/did not provide the necessary approval for your clinical trials on the Lasalocid blocks.

We request that you immediately discontinue any uses of the Bovatec premix outside of those uses covered by currently approved FDA 1800s and notify us within 10 days of receipt of this letter outlining the steps taken to prevent recurrence of the above deviations. Please direct your response to Dr. Norman R. Tufts (HFV-234), Bioresearch Monitoring Program Manager, Center for Veterinary Medicine, 5600 Fishers Lane, Rockville, Maryland 20857.

Sincerely yours,

William B. Bixler

William B. Bixler, V.M.D.
Associate Director for Surveillance
and Compliance
Center for Veterinary Medicine

cc: Mr. Art Dean
221 North Rennie
Ada, Oklahoma 74820

Mr. Harry W. Lehenbaur
RR
Kingdom City, Missouri 65265

Mr. Andy Ingram
RR # 1
Strafford, Missouri 65757

Dr. Glen A. Mente
Route 1, Box 320
Muscatine, Iowa 52761

C. K. Processing Company
Route 5
Muscatine, Iowa 52761

Hoffman-LaRoche, Inc.
Nutley, New Jersey 07110

ARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administratior
Rockville MD 20857

CERTIFIED MAIL
RETURN RECEIPT REQUESTED SEP 1 9 1985

Herbert J. Eoff, Ph.D.
Director
Animal Science Research
Hoffman-LaRoche, Inc.
340 Kingsland Drive
Nutley, New Jersey 07110

NOTICE OF ADVERSE FINDINGS

Dear Dr. Eoff:

On March 25 & 26, 1985, our Seattle Distict office inspected investigational studies conducted by Dr. David Nash, D.V.M., Simplot Livestock, Nampa, Idaho 83651, in association with Western Stockman's Supply, 2107 Industrial Road, Nampa, Idaho 83651 and Pendleton Grain Growers, Inc., Feedville and Hinkle Roads, Hermiston, Oregon 97838, utilizing the drug Lasalocid as Bovatec 68 Premix, incorporated into a free-choice medicated block under your Investigational New Animal Drug exemption (INAD) number 2422. On March 27, 1985, our Seattle District also inspected Pendleton Grain Growers, Inc., Hermiston, Oregon, in this connection.

On March 15-20, 1985, our Denver District office inspected investigational studies conducted by Dr. Ivan Rush, Scottsbluff, Nebraska 69361, and on March 13, 1985, inspected studies conducted by Mr. Dennis J. Thaler, La Grange, Wyoming 82221, and on March 14-20, 1985, inspected Hergert Milling, Inc., Scottsbluff, Nebraska 69361, in regard to use of the drug Lasalocid, as Bovatec 68 Premix, incorporated into a medicated free choice granulated mineral supplement under your Investigational New Animal Drug exemption (INAD) number 2422.

On March 14-20, 1985, our Denver District office inspected investigational studies conducted by Mr. Dean V. Radabaugh, (principal investigator) Zip Feed Mills, Inc., Sioux Falls, South Dakota 57117 with Mr. Tom Hansen, Britton, South Dakota, Mr. Don Johnannsen, Miller, South Dakota and Mr. Ken Hoxeng, Armour, South Dakota, as subsidiary investigators (conducted at eight trial locations in a four state area with individual co-operators/ranchers in charge of each site location). The studies utilized the drug Lasalocid, as Bovatec 68 Premix, incorporated into a free-choice medicated block under your Investigational New Animal Drug exemption number 2422.

On March 6-13, 1985, our Chicago District office inspected investigational studies conducted by Drs. Anthony W. Young, and Harold Woody, Southern Illinois University, Carbondale, Illinois 62901 in association with Kay Dee Feed Company, Sioux City, Iowa utilizing the drug Lasalocid, as Bovatec 68 Premix, incorporated into a free-choice medicated block under your Investigational New Animal Drug exemption (INAD) number 2422. On August 28, 1985, et. al., our Kansas City District office also inspected Kay Dee Feed Company, Sioux City, Iowa, in this connection.

se inspections have revealed serious deviations from the intent and rovisions of the new animal drug requirements of the law and regulations (Section 512 of the Federal Food, Drug, and Cosmetic Act and Title 21, Section 511.1(b) of the Code of Federal Regulations) as follows:

> Inadequate monitoring, and inadequate performance of other attendant sponsor responsibilities for these studies as evidenced by (a) drug accountability problems, such as feeding out the balance of the drug after the study had been officially terminated; (b) inaccurate reports as to the return or destruction of the drug remaining after study termination, when such drug was in fact used in animals not the subject of a controlled clinical trial; (c) significant problems regarding the lack of required records (21 CFR 511.1(b)(7)(ii); (d) failure to properly label the Lasalocid premix as required by 21 CFR 201.122(b) including the required "Caution:" statement; (e) failure to assure that the new dosage form (free choice blocks or supplements) was properly labeled as an investigational drug as required by 21 CFR 511.1(b); (f) failure to assure that required progress and final reports were submitted, 21 CFR 511.1(b)(7)(iii)); (g) failure to assure adherance to the established protocol.
>
> In addition, errors and omissions occurred in your Notice(s) of Claimed Investigational Exemptions for the Shipments of New Animal Drug, including (a) the drug on several occasions was shipped prior to providing the "Notices" to FDA (21 CFR 511.1(b)(4)) and (b) names and addresses of each clinicial investigator and cooperator and each associated feed manufacturer were not provided in all cases and/or were in error (21 CFR 511.1(b)(4)(iii)).

We are particularly concerned that future studies be appropriately monitored at the investigator and cooperator levels to assure valid data collection and that the drugs be properly labeled.

We also request that you notify us within 10 days of receipt of this letter outlining the steps taken to prevent recurrence of the above deviations. Please direct your written response to Dr. Norman R. Tufts (HFV-234), Bioresearch Monitoring Program Manager, Center for Veterinary Medicine, 5600 Fishers Lane, Rockville, Maryland 20857.

Sincerely yours,

William B. Bixler 9/15/85

William B. Bixler, V.M.D.
Associate Director for Surveillance
and Compliance
Center for Veterinary Medicine

cc: Mr. Irwin Lerner, President and Chief Executive Officer
Hoffman-LaRoche, Inc.
Nutley, New Jersey 07110

Ulw. 220

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN 11 1985

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. James H. Kent
President
Kent Feeds, Inc.
1600 Oregon Street
P. O. Box 749
Muscatine, Iowa 52761

Dear Mr. Kent:

The Food and Drug Administration recently (May 13, 1985) sent you a "Notice of Adverse Findings" regarding our Kansas City District Office inspection (March 5/7, 1985) of studies conducted by your firm and Mr. Art Dean of Ada, Oklahoma; Mr. Harry Lehenbaur of Kingdom City, Missouri; Mr. Andy Ingram of Strafford, Missouri; and Dr. Glen A. Mente of Muscatine, Iowa, utilizing the drug lasalocid (Hoffmann-La Roche, Inc.) in a medicated block. This letter replaces our letter of May 13, 1985, and reduces our level of concern regarding the inspection findings. The inspections revealed the following significant deficiencies in your research program:

1. The medicated blocks were shipped in interstate commerce without the required investigational drug labeling, including the required investigational drug caution statement.

2. You utilized a greater number of animals for clinical trials than the numbers supplied on the Notice of Claimed Investigational Exemptions for Shipment of a New Animal Drug, which was submitted to the agency by Hoffmann-La Roche.

what adopt [illegible] CT [illegible] FDA ?

Until your medicated block is approved by the Food and Drug Administration all shipments of such block are to be accompanied by an investigational new animal drug label (21 CFR Part 511.1(b)(1)). Sample labeling is contained in INAD 2422 and is available from the owner of the INAD (Hoffmann-La Roche, Inc.)

With regard to item two above, it is important that you keep us completely informed of the number of animals involved in your research effort. If after requesting a specific number of research animals you determine a need for additional animals, you should make such a request before conducting the study.

If you have questions regarding this letter, please let me know at your earliest convenience. My telephone number is (301) 443-3400.

Sincerely yours,

William B. Bixler, V.M.D.
Associate Director for
Surveillance and Compliance
Center for Veterinary Medicine

cc: Original
HFV-200 RF
HFV-120 RF
HFV-126
WMKnight, HFV-126:1jm:5/20/85
Concurred by: Dr. R. Lehmann
Dr. M. Norcross
Mr. G. Dykstra
Final:kc:6/7/85

Mr. **Weiss**. How many of these unapproved medicated blocks are on the market now, to the best of your knowledge?

Dr. **Crawford**. Well, when we find out—we don't think very many. But when we find out about them, we take action against them.

Mr. **Weiss**. In letters dated February 25, 1982, FDA notified several firms that, although the deadline had expired, interim marketing of the drugs would be permitted and that "no regulatory action is anticipated on the basis of your [medicated block's] being in unapproved status."

Mr. **Weiss**. Now, sometime subsequent to that, I assume that you changed that position.

Dr. **Crawford**. Yes. The intent in 1982 was to encourage these firms to seek approval and to allow them to continue to market until they got the approval or at least indicate whether or not they would not seek it. Some firms did not take that attitude very seriously, so we have had to have a different posture with them because they can't market it unless it is approved or unless they are seeking approval.

Mr. **Weiss**. Would you, again, for the record, submit the numbers of medicated blocks that were on the market as of 1982, including the numbers which sought and which did not seek approval.

Dr. **Crawford**. We will submit all relevant information on that topic.

[The information requested follows:]

Number of medicated block submissions as of 1982

	Number submitted
Phenothiazine	48
CTC	5
EDDI	42
Phenothiazine/EDDI	26
Total	121

We do not know how many were on the market at this time and thus those that did not seek approval.

Mr. **Weiss**. I understand that FDA is extremely concerned about the safety of sulfa drug residues, and you have commented on that a number of times in the course of your testimony today. Would you tell us why there is such concern by FDA about sulfa drug residues?

Dr. **Crawford**. Yes, Mr. Chairman. The sulfa drugs are, again, in this large category of products—by large I mean a half dozen or so—which were introduced, really, before there was a Center for Veterinary Medicine and also before there were the animal drug safety amendments.

Sulfamethazine is a persistent chemical which is difficult to use without the presence of residues over the allowable limit. We are concerned about sulfa toxicity in humans because there are a number of allergic reactions that can occur in human beings from not only these sulfas but others. There also is a suspicion that there may be other problems associated with them, such as mutagenicity and other effects on the cell. So FDA has done a number of things in order to deal with the problem.

We have commissioned a long-term study of the toxicity of sulfamethazine at our National Center for Toxicological Research in Arkansas, and that study should be completed next year. It will answer the safety questions and, more importantly, will answer the question of whether or not we can afford to raise the allowable tolerance. There are a number of authorities that think that we can. They think the product is safer than we thought it was in the 1950's when it was approved and that we can modify the allowable tolerance.

There are also a number of authorities that do not believe that sulfamethazine has the same kind of toxicological properties that we have been concerned about.

Also, in the meanwhile, we are encouraging swine producers, veterinarians and others to cooperate with FDA, USDA, and local and State authorities in lowering the numbers of swine carcasses that are contaminated with sulfamethazine. That percentage showed a marked decrease between 1978 and 1984, and now it shows a tendency to go up again. And we are trying to take steps to lower it back to acceptable limits, but we will not take final action on sulfamethazine until we receive this National Center for Toxicological Research report, which will be forthcoming in 1986.

Mr. **Weiss**. We must break now. Since we would be breaking about 2 p.m. in any event, we will conclude today's hearing and continue these proceedings tomorrow morning at 9:30.

I want to thank you, Dr. Crawford, and your other associates, for your detailed testimony and responses, and for your patience with the unavoidable interruptions that we have had.

I think that today's hearing has highlighted a number of important issues, on some of which we obviously agree and a number on which we do not.

The regulation of animal drugs is an extremely important Federal function. Our failure to do this job can jeopardize our Nation's food supply.

Unfortunately, thousands of drugs are being marketed in this country without FDA approval and, in fact, FDA has no way of knowing how many illegal drugs are out there and what animals are being given those drugs.

The drug listing program required by law has not been successful in giving FDA the information it needs to regulate this industry.

FDA and USDA have been unable, to date, to monitor the use of these illegal drugs, and the extent to which these drugs have entered our food supply.

Adequate detection methods are not yet available to assure the safety of the Nation's food supply.

FDA simply does not have the resources needed to do its job.

FDA is knowingly permitting the use of some drugs in unapproved animal species, and at unapproved doses.

The pressure for faster approval of drugs may be having a serious impact on the safety of our food.

The legitimate manufacturers of animal drugs are being placed in an unfair competitive position because of the widespread illegal manufacture, sale, and use of animal drugs.

Tomorrow, we will review FDA's regulation of several specific drugs. We look forward to your appearance, Dr. Crawford. Again I want to thank you and your associates for your participation and patience.

The subcommittee stands recessed until 9:30 a.m. tomorrow in this same room.

[Whereupon, at 1:15 p.m., the subcommittee adjourned, to reconvene at 9:30 a.m., Thursday, July 25, 1985.]

THE REGULATION OF ANIMAL DRUGS BY THE FOOD AND DRUG ADMINISTRATION

THURSDAY, JULY 25, 1985.

House of Representatives,
Intergovernmental Relations
and Human Resources Subcommittee
of the Committee on Government Operations,
Washington, DC.

The subcommittee met, pursuant to notice, at 10 a.m., in room 2154, Rayburn House Office Building, Hon. Ted Weiss (chairman of the subcommittee) presiding.

Present: Representatives Ted Weiss and Robert S. Walker.

Also present: James R. Gottlieb, staff director; Daniel W. Sigelman, counsel; Gwendolyn S. Black, secretary; and Martha Morrison, minority professional staff, Committee on Government Operations.

Mr. **Weiss**. The subcommittee will come to order. Today we continue our oversight hearings on FDA's regulation of powerful drug products used in animals raised for human consumption. Yesterday's testimony revealed that FDA may not be carrying out its full legal responsibilities for protecting the safety, quality, and wholesomeness of the American food supply.

Specifically, we heard:

That FDA cannot identify, and thus cannot regulate, the thousands of new animal drugs on the market that have never been approved as safe and effective, as required by law;

That more than 70 percent of the animal drugs and animal drug metabolites leaving residues in meat, milk, and eggs are not being monitored;

That illegal sales of highly toxic prescription veterinary drugs have gone on for several years and appear to have completely outstripped the capacity of FDA to control them;

That FDA has disregarded recommendations by its own experts to ban several carcinogenic drugs from the marketplace on the grounds that they present a potential danger to the public's health;

That FDA has established policies that violate the Food, Drug, and Cosmetic Act, and that have encouraged the illegal and potentially unsafe use of drugs by veterinary practitioners; and

That acceleration of the new animal drug approval process may have serious, unintended impacts on the safety and quality of veterinary drugs.

In continuing our examination of this critical area of FDA's responsibility, we will focus today on several regulatory situations in an effort to assess the adequacy of FDA's policies and procedures in enforcing the Nation's animal drug safety laws.

We are pleased to welcome once again the Director and Deputy Director of FDA's Center for Veterinary Medicine, Dr. Lester M. Crawford and Dr. Gerald B. Guest. Would you please take your positions at the witness table. You two gentlemen will not need to be sworn in, since you already have been sworn in.

I understand that you have some additional associates with you. Would you please approach the witness table. Dr. Tufts, Dr. Settepani, Mr. Matheson, and Dr. Zeeman. It is the practice of this subcommittee to swear its witnesses in. So before you sit down, please raise your right hand. Do you swear that the testimony you are about to give is the truth, the whole truth, and nothing but the truth?

Let the record indicate that the responses are in the affirmative.

Before we commence, Mr. Walker has advised me that some materials were entered into the record and became public documents during the course of yesterday's hearings that should not have been distributed to the public.

I will state what I think our witnesses already know. FDA carefully reviews all material it delivers to the subcommittee, before it is turned over to us.

We always ask FDA to advise us if there are specific materials that it seeks to keep confidential. We are generally pleased to honor specific FDA requests for confidentiality.

Accompanying the materials that were submitted to the subcommittee and staff were cover letters that, in essence, stated that all supplied material should be kept confidential. We have always taken the position that FDA cannot restrict public access to documents that are entered into a public hearing record on a blanket basis.

If FDA has specific concerns, it has an obligation to point them out to us, so that the subcommittee can accommodate, where possible, requests for confidentiality.

Having made that general comment, I want to call on our ranking member. First, however, I want to have Dr. Crawford make whatever comment he wants on this matter.

STATEMENT OF LESTER M. CRAWFORD, D.V.M., PH.D., DIRECTOR, CENTER FOR VETERINARY MEDICINE, FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY DR. GERALD B. GUEST, DEPUTY DIRECTOR; DR. JOSEPH A. SETTEPANI, ACTING DIRECTOR, POLICY DEVELOPMENT AND QUALITY CONTROL STAFF, OFFICE OF NEW ANIMAL DRUG EVALUATION; DR. NORMAN R. TUFTS, CHIEF, BIORESEARCH MONITORING PROGRAM STAFF, DIVISION OF COMPLIANCE, OFFICE OF THE ASSOCIATE DIRECTOR FOR SURVEILLANCE AND COMPLIANCE; JOHN C. MATHESON, CHIEF, ENVIRONMENTAL STAFF, DIVISION OF DRUG AND ENVIRONMENTAL TOXICOLOGY, OFFICE OF THE ASSOCIATE DIRECTOR FOR NEW ANIMAL DRUG EVALUATION; AND DR. MAURICE G. ZEEMAN, ENVIRONMENTAL TOXICOLOGIST, ENVIRONMENTAL STAFF, DIVISION OF DRUG AND ENVIRONMENTAL TOXICOLOGY.

Dr. **Crawford**. Yes, Mr. Chairman. I believe that you would agree that in several instances when these documents were asked for, we had cautioned the subcommittee staff that these memos could not be released to the general public, that they could be released to the subcommittee. And in and all cases, whatever you want is given to you without purgation.

Whereas under the standard format which is the Freedom of Information Act, we are obligated in order to check certain legal concerns to purge the documents, remove relevant names, and also be concerned about pending cases lest they be compromised.

And as you also know, Mr. Chairman, and had pointed out yesterday that we have to be very careful about proprietary information. And this was done over the course of the release of the documents.

Mr. **Weiss**. Well again, I do not want to repeat myself. Mr. Walker.

Mr. **Walker**. Yes, Mr. Chairman. First of all, let me say that the release of these documents was done without any consultation with the minority. The minority side was not consulted about the release of the documents, particularly to the press yesterday.

And so therefore having said that, I was to disassociate myself and the members of the minority from the action because I do not think that this is an action that can be condoned or can be blamed on the agency. It seems to me that the agency in their cover letter by describing this as confidential information put an obligation upon this subcommittee to assure that any material that it released publicly was indeed material that would not have a detrimental effect.

In this particular instance, I am led to understand and Dr. Crawford, you can correct me if I am wrong, but I am led to understand that information that was released by this subcommittee yesterday identifies undercover investigators by name—that in one case, it identifies an undercover investigator who has already expressed fear for his or her safety; that we have identified an open investigation where a company did not even know that it was under investigation and we have released documents that will probably jeopardize that particular investigation; and in addition, we have identified several pending new animal drug applications which is proprietary information. Now it seems to me that there is an appalling lack of sensitivity about the materials that we are dealing with that shows up in that kind of release of information.

But at the very least, the people responsible for handing out that information should have understood that that kind of information that identifies undercover investigators by name, for example, ought to be something that should be checked with the agency before we release it.

And I do not consider it a very bright chapter in the history of this committee which has depended upon getting information from agencies in order to conduct our investigations. If we cannot be trusted with the information, then we are going to have a difficult time obtaining information in the future.

And I for one would not blame FDA for being very suspicious in the future about giving this committee information where we show that we cannot properly manage it.

And I had pointed out in the hearing yesterday, Dr. Crawford, that I thought that you had been extremely forthright with this subcommittee. And that you were to be congratulated on what you were giving us to enable us to conduct this investigation.

I am disappointed. I am shocked to find out that the press was handed a packet of material that in fact compromises the work that you are doing. And for me at least, I apologize to you for the fact that that took place.

Mr. **Weiss**. Again just for the record, let it be stated that the only information that was distributed to the press are materials that had been entered into the public record in the course of the hearing yesterday. All of that material as soon as it is entered into the record is, in fact, properly and appropriately available to the public and to the press.

Mr. **Walker**. Well——

Mr. **Weiss**. Let me finish. I did not interrupt you. Now it is not sufficient for either the Center for Veterinary Medicine, or the FDA, or any other agency submitting materials to this subcommittee, upon reviewing and clearing such materials for delivery to us, simply to issue a generalized, blanket caution that the material may be confidential.

Since the subcommittee staff always asks FDA to identify those matters which it wants to be kept confidential, it is the agency's obligation to do that. Not having done that, it seems to me that you are hard-put after-the-fact to complain. Now, Mr. Walker, I will yield to you.

Mr. **Walker**. Thank you, Mr. Chairman. Mr. Chairman, I would simply submit to you that we have no business putting some of the documents into the public record that you put into the public record. That is the whole question. You put into the public record material that had no business getting there.

Under the standards that the gentleman is suggesting, we could have the committees of this House putting secret information that would jeopardize the national security of this Nation into the public record. That would be seen at face value as being ridiculous.

To undercut and to compromise undercover investigators who are doing valuable work on behalf of this country, I think is an appalling episode, and there is no justification for it. And the bottom line is that at the very least the agency should have been checked with having given a blanket statement of that type.

There was no check with the agency, it is my understanding, before these documents were released, and that is inexcusable.

Mr. **Weiss**. Again this subcommittee certainly has no cause to be anything other than proud of the record of confidentiality it has established over the years. The majority has never had a problem of improper or illicit disclosure of information. I think that at this point, we will proceed.

Dr. Crawford, your prepared statement cites as a major agency accomplishment—we will proceed, incidentally, on a 10-minute basis.

Mr. **Walker**. Having said that for the majority, Mr. Chairman, let me add neither has the minority.

Mr. **Weiss**. I can think of at least one specific instance. I think that the gentleman might want to reconsider that statement.

Mr. **Walker**. No; I want to say to the chairman that we had one specific instance which we referred to the Ethics Committee under a rather questionable procedure to begin with, and the Ethics Committee cleared that individual. And there were some questions raised as to the majority's conduct in that particular case, too.

So if we are going to start parading out innuendo here, let us make the record straight. The Ethics Committee upon investigation found that the gentleman, who I think you are referring to, was completly clear.

And now we have another episode before us. And I say to the gentleman that maybe we ought to follow the same procedure.

Mr. **Weiss**. If the gentleman wants to do that, he is welcome to do so at any time. I am also sure that the gentleman, should he choose, can disclose the materials in that prior matter.

Again, Dr. Crawford, your prepared statement cites as a major agency accomplishment your efforts to restrict the use of chloramphenicol.

Why do you consider this drug to be such a serious threat?

Dr. **Crawford**. Mr. Chairman, this drug is a product that is almost unique in the annals of toxicology. With most drugs that we have to contend with and most chemicals, if a certain biochemical lesion, that is disease or some damage is done to one species of animals, it is almost axiomatic that it will be done to some other species of animals. That is there is a model animal for the biochemical lesion.

In the case of chloramphenicol, it has a specific toxicity for human beings. It has been shown to cause a disease called aplastic anemia in human beings which is irreversible, untreatable, and inexorably fatal. It also has been shown to cause in those cases that survive this particular condition, that is to say aplastic anemia, leukemia.

So not only is the compound fatal on the score of toxicology in some cases, it can be fatal in terms of later developing leukemia. It is estimated by reliable toxicologists and others that approximately one in 40,000 human beings has a susceptibility which is believed to be genetic to this particular drug, and that that susceptibility is not referable to any dose or any duration of therapy or accidental exposure.

Chloramphenicol is also absorbed by virtually every route, by the oral route, by injectable routes, and even through the skin. It has therefore always been the policy of the Food and Drug Administration that the drug can be used in human medicine only with the tightest of controls, and with adequate labeling.

It has been the position of the Center for Veterinary Medicine that it can never be used in food-producing animals. That statement was first made in the 1960's when the center was quite young indeed. It has been reaffirmed lately. It has also, though, as is the case in human medicine been allowed for use in dogs and cats, and nonfood-producing animals.

It is one of the few compounds, Mr. Chairman, in closing, that is labeled not for use in food-producing animals.

Mr. **Weiss.** As I call on members of the panel for the first time, I am going to ask you to describe your responsibilities with the agency, and, to the extent you wish, state your background.

Dr. Settepani, I am going to ask you a question next. Before I do so, please tell us what your responsibilities are, and a little bit about your background.

Dr. **Settepani.** Thank you, Mr. Chairman. I was trained in chemistry. I joined FDA 10 years ago. I have always worked on the human food safety of animal drugs up until September 1, 1984. At that time, the Office of Human Food Safety was merged with the Office of Scientific Evaluation in CVM to form a new Office of New Animal Drug Evaluation. Since that time, I have been acting as Director of Policy Development and Quality Control Staff.

And my duties as director of that staff is to draft guidelines and procedural regulations that describe how we conduct our work. On the quality control, I sign off on most papers that leave the Office of New Animal Drug Evaluation. I sign off or initial off on the letters to sponsors evaluating their applications, and on approval packages that go to Dr. Crawford for final signoff.

Mr. **Weiss.** Now, Dr. Settepani, when, to your knowledge, did the Center first conclude that there was wide misuse of chloramphenicol in food-producing animals?

Dr. **Settepani.** It is hard for me to say when the center concluded this. I joined the Center for Veterinary Medicine in 1980. I spent 5 years at the Center for Foods, the Bureau of Foods then. But I can recall a research meeting in the fall of 1982, I believe, at which I discussed chloramphenicol for the first time.

It began with a discussion of a need for analytical methodology to be developed for chloramphenicol. And it then evolved into the chloramphenicol problem. And I think that Dr. Guest took an assignment then to do something about the misuse of chloramphenicol problem. At that time, as a result of that, he hired Dr. Levy, who had recently retired from the Philadelphia office of FDA, to come in and look at what was happening and what had to be done.

Mr. **Weiss.** Dr. Crawford, when did CVM receive its first recommendation to remove chloramphenicol oral solution from the market?

Dr. **Crawford.** Pursuant to the study that Dr. Levy conducted, which Dr. Settepani has just described, among the unassailable conclusions that he had drawn was that there was a form of chloramphenicol on the market which could be illegally used as an injectable solution for larger animals.

It was his conclusion that this solution was not being used in small animal medicine for which it was intended. But yet on the other hand, it offered a convenient form in an illegal means for use in food-producing animals. He drew that conclusion scientifically. As you perhaps know, the now known Levy report was extensive and made some recommendations.

That report was delivered to us in early 1984, and that is when we received the recommendation.

Mr. Weiss. I have a September 16, 1983, memorandum from Dr. Levy to the Associate Director. And I would assume that there is no disagreement that this is the report you mentioned in which Dr. Levy recommends that chloramphenicol oral solution be withdrawn from the market.

Dr. Crawford. It could have been that early. Mr. Chairman, my memory is a little later than that, but it could have been.

Mr. Weiss. Without objection, we ask that that document be entered into the record.

[The document referred to follows:]

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Associate Director, S&C, HFV-200

DATE: 9-16-83

FROM : Morris R. Levy, DVM

SUBJECT: Chloramphenicol

HISTORICAL BACKGROUND:

This drug has never been approved for use in food producing animals in the United States. Manufacturers of this drug have not submitted adequate safety data to demonstrate its safe use in food producing animals.

Chloramphenicol, a prescription drug, has been approved for use in dogs. Topical and ophthalmic preparations have been approved for both dogs and cats. Conditions associated with the use of this product are bacterial pulmonary infections, urinary tract infections, enteritis, bacterial infections of the eye, skin and those associated with canine distemper. (CFR Title 21, Part 555.110, 111, 210, 310). Further, chloramphenicol should not be administered simultaneously with penicillin or streptomycin because of potential antagonism (555.110a(iii)(e).
Chloramphenicol can only be legally sold to users on the order of a licensed veterinarian.

Our records reveal that at least 26 NADA's have been approved for chloramphenicol; 5 ophthalmic, 4 capsule, 6 tablet, 1 otic, 3 injectable, and 7 solutions. CAP tablets are currently available as 100 mg, 250 mg, 500 mg., 1 gram, 2.5 grams. CAP capsules are produced in the 50, 100, 250 and 500 mg. size. CAP injectable form is available in the 10, 30, and 200 ml vial size. CAP Palmitate Oral Suspension is sold in the 10 ml size. CAP Oral Solution is presently available in the concentration of 100 mg/ml of solutions in 100, 200, 250 mls (metric units), 4 oz (118 mls), 8 oz (236 mls) and one pint (16 oz) (473 mls) bottles. In the 250 mg/ml concentration CAP is available in the 100 ml, 200 ml (metric) and 16 oz (473 mls) bottle size (memo J. R. McDowell, DVM, to Max Crandall, DVM, dated July 19, 1983).

The chloramphenicol oral solution is bitter tasting and inappropriate for dosing except by stomach tube.

Propylene glycol is the most frequently used vehicle in the CAP oral solutions.

We have become aware of the widespread use of the CAP oral solution converted to an injectable to treat feedlot and dairy cattle as well as veal calves. This is apparently an attempt to avoid the more expensive available injectable chloramphenicol product (CAP + succinate ester). (A.P. Knight, J.A.V.M.A. Vol. 178, 2-1-81 P. 309-10). We have also been alerted to the use of chloramphenicol therapy ~~for mastitis.~~ (Ben Stroud, DVM - USDA Beltsville, MD 8-15-83 - Personal communication). Feedlots tend to avoid oral administration of chloramphenicol due to rumen flora interference and erratic CAP absorption.

The oral solution has been recommended to be given IV, IM or subcutaneously twice daily in dairy cattle with 8 to 10 grams dosages; 2 grams to be injected into the teat quarters (R. W. Meiring, D.V.M., 18th Annual Meeting, National Mastitis Council, Louisville, KY, Feb. 19-21, 1979).

HFD 332 provides the statistics for certified batches of chloramphenicol oral solutions as follows: June 1969 to April 1981
512, 969/16 ounce bottles consisting of:
100 mg/ml 76 batches = 22,425.74 Kg
250 mg/ml 9 batches = 6,949.55 Kg
29,375.29 Kg.

Compilation of DER Submissions from 4-23-82 to 3-1-83 from five (5) manufacturers holding NADAs for CAP Oral Solution:
260,747-16 oz (473 ml) bottles

and
21,747-12 oz (355 ml) bottles were offered for marketing.

An audit inspection(4-7-82) of Philips Roxane, St. Louis, MO by Kansas City District to determine distribution of chloramphenicol oral solution to distributors and veterinarians revealed that at least one customer, Sterling and Sons, Denver, Colorado distributed 2400/16 ounce bottles of CAP oral solution from Dec. 1981 to Feb. 1982 to a feedlot, Foxley Cattle Co., Ordway, Colorado c/o of the firm's consulting veterinarian.

An NAF (Notice of Adverse Findings) letter issued by Denver District (Oct. 7, 1982) received a reply from the firm's veterinarian, (Oct. 16, 1982) that the chloramphenicol was used to treat Pasteurella hemolytica, a pathogen which he stated was only sensitive to chloramphenicol.

We can only assume that the numerous veterinarians receiving large shipments of CAP oral solution from distributors would utilize these large amounts of CAP to treat food producing animals.

Obviously the availability of the 16 ounce size bottles of CAP oral solution has facilitated extensive and promiscuous use by veterinarians engaged in food animal medicine.

Numerous articles have been appearing in foreign and domestic professional journals that discuss and lend credence to the usefulness of the CAP oral solution as an injectable in food animal medicine despite the lack of safety data and potential toxicity to animals (Knight, JAVMA, Vol. 178, 2/1/81 Pg 309-310) and man (aplastic anemia, et al), and absence of FDA clearance for use of this product in food producing animals.

USDA/FSIS presently has an acceptable methodology to ascertain the presence of chloramphenicol in the tissues of slaughtered animals. This method appears to have been properly validated. USDA is willing to defend this method in court with their analysts as witnesses if a legal issue arises for an FDA action.

USDA/FSIS will, no doubt, extend their analytical coverage for CAP analyses of slaughtered livestock. Recently USDA reported the presence of illegal residues of CAP in the tissues of two (2) calves sold to auction markets in California. One calf showed a level of 5.77 ppm CAP in the muscle tissue, the other 8.3 ppm CAP in the muscle tissue, both findings were confirmed by mass spectrometry.

DISCUSSION:

1. There does not appear to be any rationale for the 1 pint (16 oz) size bottle of the CAP oral solution in the practice of canine medicine. The CAP oral solution is bitter tasting and properly administered to the canine only via stomach tube, a tedious, difficult procedure, not likely to be followed in practice. This product readily lends itself to illegal parenteral use in feedlot and dairy cattle, veal calves and probably in other food producing animals (swine?).

2. Evidence has accumulated that the sale and distribution of the 16 oz. size bottles of CAP oral solution to feedlot veterinarians and veterinarians engaged in general food animal practices continues to grow. We are aware that all other size bottles of CAP oral solutions could be substituted and used parenterally if the 16 ounce size is withdrawn. To preclude this from happening and since we cannot justify continuation of the manufacture and marketing of CAP oral solution for treatment of dogs unless reformulated, all product forms of CAP oral solution (this would not include CAP Palmitate Oral Suspension) should be withdrawn.

3. Public health concerns continue to grow that illegal residues resulting from the unabated use of this product in food animals could be adding to serious human health hazards already attributed to chloramphenicol (e.g. probable drug sensitivities that can lead to anaphylactoid reactions, transferability of drug resistance from animals to man or even aplastic anemia). The literature indicates that aplastic anemia in humans is non-dose related (CAP). Even CAP ophthalmic product use has been linked ~~to the development of~~ . . . . . aplastic anemia in humans.

RECOMMENDATIONS:

It is our firm recommendation that a **FEDERAL REGISTER** notice issue from the Bureau of Veterinary Medicine containing the following basic elements:

1. All chloramphenicol oral preparations other than Chloramphenicol Palmitate Oral Suspension be withdrawn from production and marketing for treatment of dogs for the following reasons:

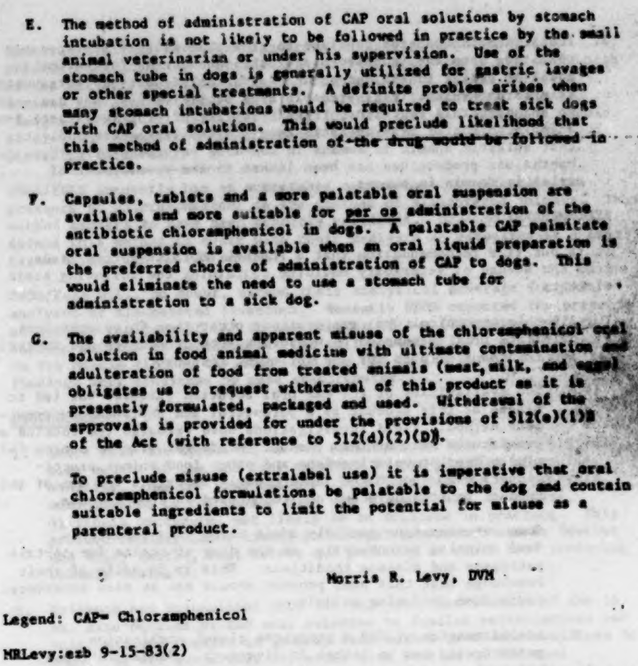
   A. The availability of the CAP Oral Solution (Liquid) has led to misuse of this product as a parenteral and intramammary treatment method. Field investigations have revealed the routine and promiscuous sale of this product (preferred size 16 ounces (473 mls)to feedlot veterinarians and other food animal practitioners even though the label clearly restricts the use of this product to dogs only and not to be used in food animals.

   Some veterinarians candidly admit using this product in food animals, parenterally, as the drug of choice for certain pathogens and disease conditions. This is in spite of their knowledge that this oral product should not be used parenterally or in food producing animals.

   B. Administration of CAP + propylene glycol combination parenterally can be lethal to livestock. Sudden collapse, hemolysis, anemia and even death have been observed when CAP-propylene glycol combinations have been administered IV (Knight JAVMA. Vol. 178, 2/1/81, pg. 309-310).

   C. USDA/FSIS has already reported the presence of illegal residues of chloramphenicol in food animals. We can expect a more active interest by USDA/FSIS in sampling tissues from slaughtered animals for the presence of CAP in the near future.

   D. Commercially available CAP oral solutions dissolved in propylene glycol bases are bitter-tasting and unpalatable to dogs. Any oral chloramphenicol preparations approved in the future should be palatable and not lend themselves to misuse.



E. The method of administration of CAP oral solutions by stomach intubation is not likely to be followed in practice by the small animal veterinarian or under his supervision. Use of the stomach tube in dogs is generally utilized for gastric lavages or other special treatments. A definite problem arises when many stomach intubations would be required to treat sick dogs with CAP oral solution. This would preclude likelihood that this method of administration of ~~the drug would be followed in~~ practice.

F. Capsules, tablets and a more palatable oral suspension are available and more suitable for per os administration of the antibiotic chloramphenicol in dogs. A palatable CAP palmitate oral suspension is available when an oral liquid preparation is the preferred choice of administration of CAP to dogs. This would eliminate the need to use a stomach tube for administration to a sick dog.

G. The availability and apparent misuse of the chloramphenicol oral solution in food animal medicine with ultimate contamination and adulteration of food from treated animals (meat, milk, and eggs) obligates us to request withdrawal of this product as it is presently formulated, packaged and used. Withdrawal of the approvals is provided for under the provisions of 512(e)(1)B of the Act (with reference to 512(d)(2)(D)).

To preclude misuse (extralabel use) it is imperative that oral chloramphenicol formulations be palatable to the dog and contain suitable ingredients to limit the potential for misuse as a parenteral product.

Morris R. Levy, DVM

Legend: CAP= Chloramphenicol

MRLevy:ezb 9-15-83(2)

Mr. Weiss. Wasn't a Notice of Opportunity for Hearing [NOOH] to withdraw chloramphenicol oral solution from the market initially drafted even before that time by Dr. Beaulieu?

Dr. Crawford. We do not know the answer to that. It could have been in a draft form and not elevated to my attention, Mr. Chairman.

Mr. Weiss. I have here an August 31, 1983, draft by Dr. Beaulieu recommending that an NOOH be published withdrawing the approval of chloramphenicol oral solution.

[The document referred to follows:]

Director, BVM, HFV-1

DRAFT

THRU: Associate Director, S&C, HFV-200

Director, Division of Surveillance, HFV-210

Chloramphenicol Oral Solutions - ACTION

DISCUSSION

Evidence has been building for some time concerning the use of chloramphenicol in food producing animals. There is no question that such use is now a common practice. There is also every reason to believe that the principle source of the chloramphenicol going into food producing animals in this country is the currently approved oral solutions labeled for use in dogs. In fact these products are far better suited to misuse in food animals than to use in dogs. They are so bitter that they can only be administered by stomach tube, a far from routine route of administration of drugs in canine practice.

Misuse of chloramphenicol in food producing animals constitues a serious potential health hazard for the consumers of this country. Adverse effects are life threatening, no-effect levels have not been demonstrated, therefore, withdrawal periods have not been established and initial monitoring by USDA has detected residues well above the level of sensitivity of the method currently in use. These levels approach, and in a few cases surpass, levels known to cause aplastic anemia in humans.

It is clear that the potential hazards associated with these products as actually used far outweigh any benefits to be derived from their intended use. On this basis, the products should be withdrawn. The canine practitioners of this country will be negligibly affected by removal of these products from the market. Food animal practitioners will be denied a readily available and relatively inexpensive source of chloramphenicol, the use of which in food animals is illegal. Consumers will benefit to the extent that use of chloramphenicol in food producing animals, and subsequent drug residues and health hazards, are curtailed.

To the best of our knowledge, BVM has never withdrawn approval of any NADA solely, or even principally, on the basis that the hazards associated with misuse outweighed any possible benefits associated with intended use. We believe, however, that the FD&C Act clearly provides a basis for such action. Safety assessment is associated with the likelihood that intended conditions of use will be followed in practice in 512(d)(2)(D). While this criterion only appears under reasons for refusing to approve, it is apparent that it also must be a criterion for withdrawal since in the first case one is dealing with hypothetical misuse and in the latter with demonstrated misuse . (If the weaker of the two cases supports refusal to approve, the stronger must support withdrawal.)

We therefore propose withdrawal of applications providing for the approval of chloramphenicol oral solution under the provisions of 512(e)(1)(B) with reference to 512(d)(2)(D) (to define the term safety as used in 512(e)). We believe the case can successfully be made that it is highly unlikely that the intended conditions of use will be followed in practice and furthermore that for significant amounts of the product they are not being followed in practice.

Failure to act against these products undermines our Extralabel Use Policy because these products have traditionally constituted the most significant source of chloramphenicol used in food-producing animals. Failure to remove this source could be interpreted as lack of resolve on our part to curtail extralabel use, particularly since these products are so blatantly misused.

We believe that the effort to remove these products, once publicized, will reinforce our extralabel use policy and may in itself, have a salutary effect. Actual removal of the products will eliminate a significant source of misused drug from the market. We cannot guarantee that other sources will not subsequently be tapped; however, other sources are either less convenient, more expensive, or both. Those veterinarians who choose to go to the extreme of smuggling unapproved chloramphenicol to meet their perceived needs can, and should, be prosecuted on that basis.

It should be noted that for reasons not clear, the oral solutions were approved as "me-too" applications to Parke-Davis' NAS/NRC reviewed oral suspension. (NADA 55-047). While it may superficially appear strange to propose to withdraw only the "me-too" applications and not the parent product, this proposed withdrawal is based on product misuse and the oral suspension is not, to the best of our knowledge, misused in food-producing animals. Furthermore, it is practical for its intended use in dogs. The risk/benefit assessment for this product is, therefore, entirely different and withdrawal of the oral suspension is not warranted, at this time.

CONCLUSIONS

1. There is no unique need for, or benefit derived from, oral chloramphenicol solutions intended for use in dogs relative to other available dosage forms; in fact, due to their lack of palatability and need for stomach tube administration, they are far less useful in dogs than other available dosage forms (ie. capsules, tablets, oral suspension, and injectable).

2. Therefore, no significant loss would accrue to canine practitioners if oral chloramphenicol solutions were removed from the market. One or more of the other currently available dosage forms could meet any existing need for chloramphenicol in canine practice.

3. Significant amounts, probably almost all, of the chloramphenicol oral solution distributed in this country is actually injected (or infused) into food producing animals.

4. Misuse of chloramphenicol in food producing animals constitutes a serious potential health hazard for the consumers of this country.

5. The risks associated with the marketing of these products far exceed the benefits derived.

6. Approval to market the following products should be withdrawn.

   NADA 55-003 Tevcocin Oral Solution (withdrawal voluntarily requested by IMF)

   NADA 65-364 Veticol Oral Solution (Copanos)

   NADA 65-464 Chloramphenicol Oral Solution (Pfizer)

   NADA 65-477 Anacetin Oral Solution (Philips-Roxane)

   NADA 65-484 Chloramphenicol Oral Solution (Michael Gordon)

   NADA 65-487 Chloramphenicol Oral Solution (Medico)

RECOMMENDATION:

1. The attached Notice of Opportunity for a Hearing should be signed and the document published as soon as possible.

Andrew J. Beaulieu, DVM

cc:

HFV-1 HFV-2 HFV-100 HFV-200 HFV-300 HFV-220 HFV-230 HFV-214

AJBeaulieu:ezb 11-9-83(19)

Retyped: 8-31-84(19)

Mr. WEISS. About the same time, different people in the agency were making similar recommendations.

When did FDA actually publish such a Notice of Opportunity for Hearing?

Dr. CRAWFORD. Just this past month. May I also say that it was part of an overall strategy. Perhaps you have a follow-up question, but I would like to reserve—may I proceed on that line?

Mr. WEISS. Please.

Dr. CRAWFORD. OK. Actually what happened is that once we determined that this oral solution was a problem, we attempted to develop a strategy to bring it to the attention of the manufacturers and other persons that may be involved in this process. And that took two forms. One is a letter to veterinarians who may be using the product illegally.

As mentioned yesterday, in March 1984, we sent letters to all veterinarians specifically warning them personally of the dangers of using it and the illegality of using it, and promising follow-up regulatory action. At the same time, Mr. Chairman, in the spring of 1984, we wrote letters to the manufacturers of the oral solution bringing this to their attention, and telling them that the continuation of the approval of this product was not likely, and would they consider voluntary withdrawal.

We received some responses which were in the affirmative, some which seemed to be in the negative, and some which seemed to be in between. We continued to negotiate with these companies to get them to voluntarily take it off the market.

And once it became apparent that that was not going to take place in all cases, we put forth the Notice of an Opportunity for Hearing, which I mentioned was published this month.

Mr. WEISS. I must say that, given the description that you gave at the outset as to the hazards presented by this particular drug, I cannot understand why it would have taken FDA almost 2 years to publish the Notice of Opportunity for Hearing.

You testified that, from the beginning, the drug was prohibited for use in animals raised for human consumption. Isn't that right?

Dr. CRAWFORD. Yes.

Mr. WEISS. So it is not as if FDA was unaware of the dangers of this drug. You discovered at least 2 years ago that it was being widely used for unapproved purposes in food-producing animals. Yet it takes you 2 years before you publish a Notice of Opportunity for Hearing. I do not understand that.

Dr. CRAWFORD. Let me explain that. What happens is that a Notice for an Opportunity for a Hearing avails these firms that have the drug on the market to take advantage of a hearing. It also gives them the right to say that they do not need to have a hearing, and we can take it off the market.

The process though, the administrative hearing process involved takes a long period of time, as I mentioned yesterday, during which time the product is not off the market in any case. It is only off the market once the administrative hearing is completed, and is completed in our favor.

We thought that since the product was approved and labeled for dogs and cats, and since it only goes through veterinarians' hands, we needed to take a three-pronged approach. Not just the prolonged administrative hearing process, but we needed to see if we could not cut down on distribution of the drug by having some companies and hopefully all cease marketing it. In fact, some of them did.

We also wanted to inform veterinarians that they should not be involved in the diversion of this product to the food-producing animals. We believe that that effort has been largely successful.

Also, we wanted to take regulatory action against the product where we could find it being destined for food-producing animal use, and we have done a great deal of that over the period of time.

Mr. **Weiss**. So the product is still on the market?

Dr. **Crawford**. The product is still on the market by some companies.

Mr. **Weiss**. Assuming that you prevail in the withdrawal hearing, how long do you think it will be before the withdrawal hearing is completed and the drug will be removed from the market?

Dr. **Crawford**. The firms have a certain amount of time to respond to the Notice, which I believe is 60 days. They have 60 days, the firms, to respond with evidence that a hearing is necessary. Then we evaluate that and make the decision as to whether or not there will be a hearing.

They also have the opportunity to say that they do not wish to contest, and therefore they will submit their NADAs for cancellation. That is always a possibility, and one which we hope will obtain. If that is the case, Mr. Chairman, then the product will be off the market by the end of this year.

If the firms contest and if they offer reasonable evidence that they can keep the product in small animal non-food-producing animal channels, and we still go forward with the hearing, then it could take as long as a year and maybe more from now.

Mr. **Weiss**. Are there other forms of chloramphenicol on the market besides the oral solution?

Dr. **Crawford**. Yes. There are a number of human medical products. There is an ocular solution, ophthalmic drops and ointment. There is also an injectable human solution. There are tablets and capsules. And in veterinary medicine for nonfood animal use, there is roughly the same spectrum of products.

Mr. **Weiss**. Since the oral solution which is labeled for cats and dogs has been illegally diverted to use in food-producing animals, have you anticipated the possible misuse of these other forms, and, if so, what do you intend to do to foreclose such misuse?

Dr. **Crawford**. That is a good question, Mr. Chairman, because we have evaluated all those forms, and our conclusions are as follows. We cannot document diversion of products other than this oral solution into food-producing animal use. Now there are several reasons for that. Roughly speaking, it is because they are not packaged in such a way as to be convenient to use in large animals.

There is another product that we are concerned about, though, and that is a product that is basically the same as the oral solution that is added to control disease in pet fish in the aquariums. And as you would know, persons who would have home aquariums using this product would be exposed to it through their hands and so forth, and we are taking direct action against that product to get it off of the market.

It is not an approved product. It is one of those that we discussed yesterday that apparently has fairly recently come on the market. We found out about its use, and we are involved in regulatory action with the firm that is manufacturing it at the present time.

Mr. **Weiss**. Is it possible for you to forewarn the manufacturers and the veterinary medicine field of your concern about the possible misuse of forms other than the oral solution, such as the tablet or capsule?

Dr. **Crawford**. Yes, it is.

Mr. **Weiss**. Well, I would hope that you would attempt to take steps to so advise them. Otherwise, you may be finding yourself moving from one form of misuse to another.

Incidentally, an inspection of a veterinary clinic in New York, I understand, has already found misuse of 1 gram chloramphenicol tablets. And the Kansas City field office has had reports of misuse of the 500 milligram capsules, whose contents are emptied and made into an injectable. So misuse of forms other than the oral solution has already been documented.

[Supporting documents follow:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date March 26, 1984

From Director Division of Compliance (HFV-230)
Bureau of Veterinary Medicine

Subject DOC 84-380-130 Chloramphenicol Sodium Succinate for Injection
DOC 84-380-131 Anacetin (Chloramphenicol) Tablets
LAM# 11361

To Case Management Section (HFC-25)
Through: Associate Director (Acting) Surveillance and Compliance, (HFV 200) 3/26/84
Through: Director, Bureau of Veterinary Medicine, (HFV-1) 3/29/84

Firm: Perry Veterinary
Clinic
Perry, NY

SEIZURE APPROVED

As a result of an investigation of an illegal residue (streptomycin and neomycin) in a cow from Ru-Ann Holsteins, Inc., Avon, NY, BUF-DO become aware of the use of chloramphenicol in food producing animals (dairy cows). Investigation revealed stocks of chloramphenicol oral solution and Chloromycetin Sodium Succinate, which had been obtained from Perry Veterinary Clinic, on the farm, and clear indications that the drugs had been used in dairy cows for the treatment of pneumonia, high fever and/or mastitis. Followup investigation at the Perry Veterinary Clinic on 12/5, 6, 8, 12 and 13/83 revealed that the veterinarians were using chloramphenicol (oral and injectable) to treat food producing animals routinely. A mastitis preparation, Formula 111, contained Chloramphenicol Sodium Succinate in addition to ampicillin. The veterinarians associated with this clinic freely admitted use of the chloramphenicol drugs in their treatment of dairy cows. While the veterinarians instruct the users to withhold milk for 5 days after treatment and for 100 days for slaughter for meat, there is no assurance that these instructions are adequate to prevent illegal chloramphenicol residues.

While the veterinarians interviewed during the investigation of Perry Veterinary Clinic indicated that chloramphenicol will not be used in the future, there is no assurance that current stocks of the drugs will not be misused.

Chloramphenicol is a toxic antibiotic substance with a narrow safety margin in humans. Serious adverse reactions in humans such as fatal anemia, "gray syndrome" in premature and newborn infants, gastrointestinal, neurotoxic and hypersensitivity reactions can occur. Aplastic anemia in humans is not dose-related. This usually fatal type of blood dyscrasia has been associated with extremely low levels of exposure to chloramphenicol by a significant subgroup of the population with an apparent predisposed sensitivity to the drug. The human hazards of the drug are clearly stated in the required label warning for human labeled chloramphenicol (See labeling for DOC 84-380-130). All approved chloramphenicol products for animal use bear a label warning against use in food producing animals.

Chloromycetin Sodium Succinate (Chloramphenicol Sodium Succinate 1 gram per vial) bears the human Rx legend. ~~However, the~~ intended use in the possession of these veterinarians is clearly for food animals. Affidavits from veterinarians (De Groff, Wiseley) clearly indicate that the drug is intended for use in animals. Because the drug contains chloramphenicol, it is defined in 201(w)(3) as a new animal drug and the lack of labeling indication for animal use would not lessen the NAD status. There is no appoval for the use of the Chloramphenicol Sodium Succinate product in food producing animals and the new animal drug is unsafe within the meaning of section 512(a)(1)(A) for the purposes of section 501(a)(5).

A section 502(f)(1) violation exists with respect to the human labeled product in that the labeling bears no directions for animal use. However a part of C.V.M. Management prefers not to use this charge due to the possibility of raising the issue of calling human drugs in the possession of veterinarians as illegal on its face.

Anacetin (Chloramphenicol) 1 gram tablets are the subject of an approved NADA 65-461 held by Philips Roxane Inc., St. Joseph, MO, which is codified at 21 CFR 555.110a. However, the approval does not provide for use in food-producing animals therefore the drug is adulterated [501(a)(5)] since it is unsafe within the meaning of §512(a)(1)(A) because no approval is in effect for such use.

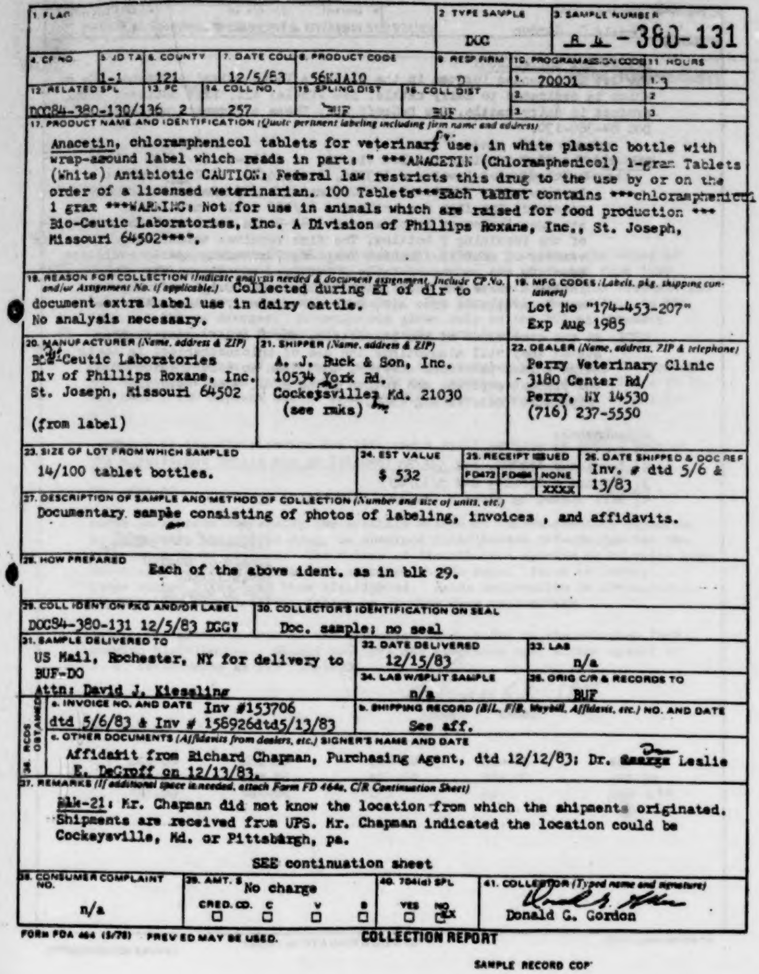
Allegedly, the veterinarians will not continue to use the chloramphenicol products in food producing animals, however, we do not have assurance that this will be the case. Therefore, we concur in Buffalo District's recommendation for seizure of the stocks of chloramphenicol, in the possession of licensed veterinarians, which have been used in food producing animals. We recognize that the veterinarians can file claim for the goods and possibly institute controls within the context of a Consent Decree which would prevent possible use in food-producing animals. Note that the affidavit from Dr. DeGroff, and CR4DOC 84-380-130 indicate that Chloromycetin Sodium Succinate was received via UPS; however, further investigation revealed it was received via Oneida Motor Freight Truck.

This is not a routine case, since it is an initial effort to seize adulterated and misbranded chloramphenicol drugs in the possession of a licensed veterinarian. We feel such an action is necessary to protect the public health and clearly delineate the BVM position on the use of chloramphenicol in food producing animals. BVM will provide the necessary expert witness support as needed. James E. Tessmer (HFV-236) is the Consumer Safety Officer assigned this case.

Edward J Ballitch

Edward J. Ballitch
Director Division of Compliance
Bureau of Veterinarian Medicine

cc: HFR-2200
HFR-2240
HFR-21
HFO-410
HFC-20
HFV-200
HFV-210
HFV-214
HFV-230(2)
HFV-236(HR/RS 4-012)
HFV-400
HFA-224
JETessmer:rl:3/5/84
initialed by DNScarr(as revised) 3/19/84
initialed by JBeaulieu(as revised) 3/19/84
initialed by WBBixler (as revised) 3/21/84



1. FLAG				2. TYPE SAMPLE DOC	3. SAMPLE NUMBER 84-380-131	
4. CF NO	5. JD TA 1-1	6. COUNTY 121	7. DATE COLL 12/5/83	8. PRODUCT CODE 56KJA10	9. RESP FIRM D	10. PROGRAM ASSIGN CODE 1. 70001 2. 3.	11. HOURS 1. 3 2 3
12. RELATED SPL DOC84-380-130/136	13. PC 2	14. COLL NO. 257	15. SPLING DIST BUF	16. COLL DIST BUF		

17. PRODUCT NAME AND IDENTIFICATION (Quote pertinent labeling including firm name and address)

Anacetin, chloramphenicol tablets for veterinary use, in white plastic bottle with wrap-around label which reads in part: " ***ANACETIN (Chloramphenicol) 1-gram Tablets (White) Antibiotic CAUTION: Federal law restricts this drug to the use by or on the order of a licensed veterinarian. 100 Tablets***~~Each tablet~~ contains ***chloramphenicol 1 gram ***WARNING: Not for use in animals which are raised for food production *** Bio-Ceutic Laboratories, Inc. A Division of Phillips Roxane, Inc., St. Joseph, Missouri 64502***".

18. REASON FOR COLLECTION (Indicate analysis needed & document assignment. Include CP No. and/or Assignment No. if applicable.) Collected during EI of dlr to document extra label use in dairy cattle. No analysis necessary.

19. MFG CODES (Labels, pkg, shipping containers)
Lot No "174-453-207"
Exp Aug 1985

20. MANUFACTURER (Name, address & ZIP)
Bio-Ceutic Laboratories
Div of Phillips Roxane, Inc.
St. Joseph, Missouri 64502

(from label)

21. SHIPPER (Name, address & ZIP)
A. J. Buck & Son, Inc.
10534 York Rd.
Cockeysville, Md. 21030
(see rmks)

22. DEALER (Name, address, ZIP & telephone)
Perry Veterinary Clinic
3180 Center Rd/
Perry, NY 14530
(716) 237-5550

23. SIZE OF LOT FROM WHICH SAMPLED: 14/100 tablet bottles.

24. EST VALUE: $ 532

25. RECEIPT ISSUED: FD472 ☐ FD484 ☐ NONE XXXX

26. DATE SHIPPED & DOC REF: Inv. # dtd 5/6 & 13/83

27. DESCRIPTION OF SAMPLE AND METHOD OF COLLECTION (Number and size of units, etc.)
Documentary sample consisting of photos of labeling, invoices , and affidavits.

28. HOW PREPARED
Each of the above ident. as in blk 29.

29. COLL IDENT ON PKG AND/OR LABEL: DOC84-380-131 12/5/83 DGG

30. COLLECTOR'S IDENTIFICATION ON SEAL: Doc. sample; no seal

31. SAMPLE DELIVERED TO
US Mail, Rochester, NY for delivery to
BUF-DO
Attn: David J. Kiessling

32. DATE DELIVERED: 12/15/83

33. LAB: n/a

34. LAB W/SPLIT SAMPLE: n/a

35. ORIG C/R & RECORDS TO: BUF

36. RCDS OBTAINED

a. INVOICE NO. AND DATE: Inv #153706 dtd 5/6/83 & Inv # 156926dtd5/13/83

b. SHIPPING RECORD (B/L, F/B, Waybill, Affidavit, etc.) NO. AND DATE: See aff.

c. OTHER DOCUMENTS (Affidavits from dealers, etc.) SIGNER'S NAME AND DATE: Affidavit from Richard Chapman, Purchasing Agent, dtd 12/12/83; Dr. ~~[illegible]~~ Leslie E. DeGroff on 12/13/83.

37. REMARKS (If additional space is needed, attach Form FD 464a, C/R Continuation Sheet)

Blk-21: Mr. Chapman did not know the location from which the shipments originated. Shipments are received from UPS. Mr. Chapman indicated the location could be Cockeysville, Md. or Pittsburgh, pa.

SEE continuation sheet

38. CONSUMER COMPLAINT NO.: n/a

39. AMT. $ No charge
CRED. CO. ☐ C ☐ V ☐ S ☐

40. 704(a) SPL: YES ☐ NO ☒

41. COLLECTOR (Typed name and signature)
Donald G. Gordon

FORM FDA 464 (5/78) PREV ED MAY BE USED. COLLECTION REPORT

SAMPLE RECORD COPY

1. COLLECTOR (Print or type name)	2. DISTRICT	3. C/R NO.	4. DATE COLLECTED
Donald C. Gordon	BUF	DOC84-380-131	12/5/83

5. REMARKS

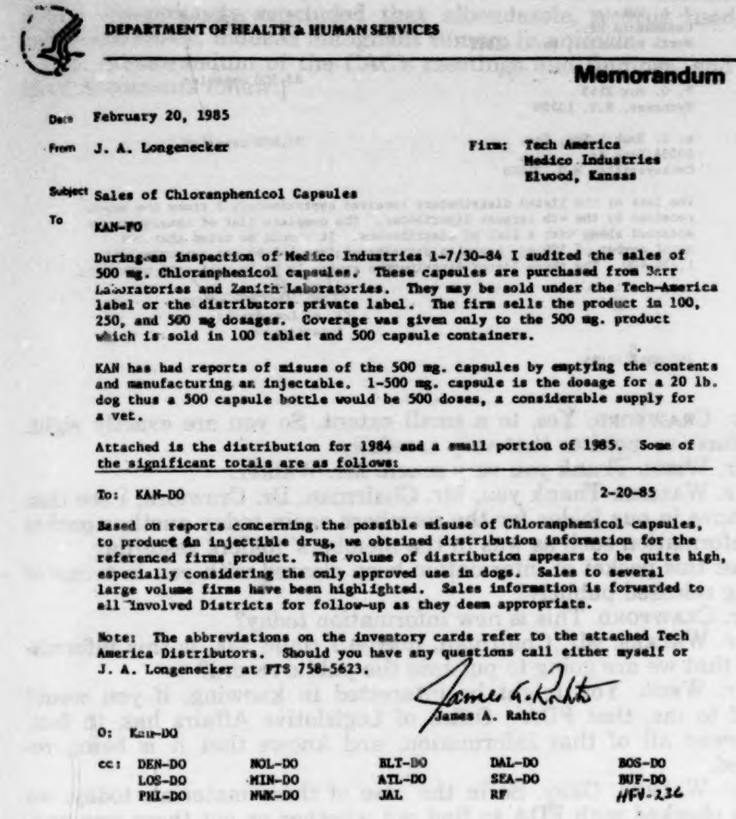
Reason for Collection:
The lot is intended for use in the clinic's large animal practice, 98% of which is dedicated to dairy cattle. See Wiseley aff. Firm admitted using product in dairy cattle. See DeGroff aff. These affidavits are attached to DOC 84-380-130.

Blk 36: The firm received the lot via UPS as follows: 1) 5/100 tablet bottles under invoice # 153706, dtd 5/6/83. 2) 7/100 tablet bottles under Invoice # 158926, dtd 5/13/83. Copies of Invoices attached. The firm currently has 14/100 tablet bottles in storage. Review of Invoices for ~~1982-3~~ did not reveal the source of the remaining 2 bottles. The firm receives animal drugs from a ~~xa~~ variety of sources. Richard Chapman, Purchasing Agent, could not identify the source of these 2 bottles, nor did he know the ~~xxxxx~~ location where the 2 shipments originated. Origin of shipments may be available from A.J. Buck & Son, Inc., Cockeysville, Md.

NOTE: At the conclusion of the inspection, the 8 staff veterinarians stated they will discontinue the use of chloramphenicol in their large animal practice. However, they plan to hold the lot until the product expires, and return it to A. J. Buck. Note the expiration date is Aug 1985.

Attachments:
1) Photos of labeling
2) Invoice # 153706, dtd 5/6/83
3) Invoice # 158926, dtd 5/13/83
4) Aff. signed by Richard Chapman, Purchasing Agent.

Donald C. Gordon
Investigator
BUF-DO Roch RP



DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date February 20, 1985

From J. A. Longenecker

Firm: Tech America
Medico Industries
Elwood, Kansas

Subject Sales of Chloranphenicol Capsules

To KAN-FO

During an inspection of Medico Industries 1-7/30-84 I audited the sales of 500 mg. Chloranphenicol capsules. These capsules are purchased from Barr Laboratories and Zanith Laboratories. They may be sold under the Tech-America label or the distributors private label. The firm sells the product in 100, 250, and 500 mg dosages. Coverage was given only to the 500 mg. product which is sold in 100 tablet and 500 capsule containers.

KAN has had reports of misuse of the 500 mg. capsules by emptying the contents and manufacturing an injectable. 1-500 mg. capsule is the dosage for a 20 lb. dog thus a 500 capsule bottle would be 500 doses, a considerable supply for a vet.

Attached is the distribution for 1984 and a small portion of 1985. Some of the significant totals are as follows:

To: KAN-DO 2-20-85

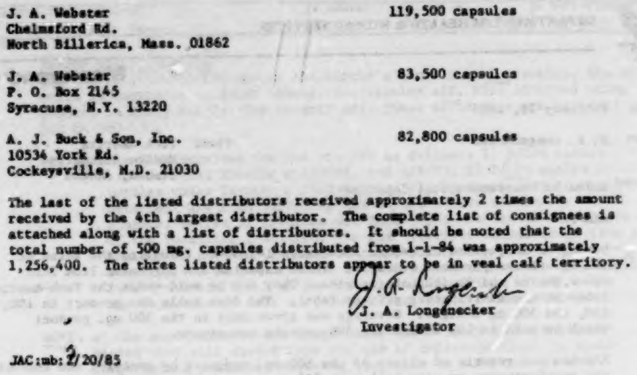
Based on reports concerning the possible misuse of Chloranphenicol capsules, to produce an injectible drug, we obtained distribution information for the referenced firms product. The volume of distribution appears to be quite high, especially considering the only approved use in dogs. Sales to several large volume firms have been highlighted. Sales information is forwarded to all involved Districts for follow-up as they deem appropriate.

Note: The abbreviations on the inventory cards refer to the attached Tech America Distributors. Should you have any questions call either myself or J. A. Longenecker at FTS 758-5623.

James A. Rahto
James A. Rahto

O: Kan-DO

cc: DEN-DO NOL-DO BLT-DO DAL-DO BOS-DO
LOS-DO MIN-DO ATL-DO SEA-DO BUF-DO
PHI-DO NWK-DO JAL RF #FV-236



J. A. Webster Chelmsford Rd. North Billerica, Mass. 01862	119,500 capsules
J. A. Webster P. O. Box 2145 Syracuse, N.Y. 13220	83,500 capsules
A. J. Buck & Son, Inc. 10534 York Rd. Cockeysville, M.D. 21030	82,800 capsules

The last of the listed distributors received approximately 2 times the amount received by the 4th largest distributor. The complete list of consignees is attached along with a list of distributors. It should be noted that the total number of 500 mg. capsules distributed from 1-1-84 was approximately 1,256,400. The three listed distributors appear to be in veal calf territory.

J. A. Longenecker
Investigator

JAC:mb: 2/20/85

Dr. CRAWFORD. Yes, to a small extent. So you are exactly right. We have to monitor that very carefully.

Mr. WEISS. Thank you very much. Mr. Walker.

Mr. WALKER. Thank you, Mr. Chairman. Dr. Crawford, I see that we have in our folder for the members again today another packet of information such as was in the members' folders yesterday.

Has this packet of information been cleared with you in terms of being released publicly?

Dr. CRAWFORD. This is new information today?

Mr. WALKER. Mr. Chairman, maybe I could ask, is this information that we are going to put into the public record?

Mr. WEISS. You might be interested in knowing, if you would yield to me, that FDA's Office of Legislative Affairs has, in fact, reviewed all of that information, and knows that it is being released.

Mr. WALKER. Okay. So in the case of these materials today, we have checked with FDA to find out whether or not there was anything that was sensitive in them with regard to release?

Dr. CRAWFORD. Excuse me. Actually, the Office of Legislative Affairs said that they only had 5 or 10 minutes to review them. We would like the opportunity and would be pleased, Mr. Chairman, with your permission to review them now prior to release. They would like very much to be able to do that.

Mr. WALKER. I would ask unanimous consent, Mr. Chairman, that the agency be given permission to review these documents today given the incident of yesterday prior to any public release of the documents.

Mr. WEISS. I have no problem with Ms. Richardson, or whoever else Dr. Crawford chooses, to look over them. If they find any matter that they overlooked previously, they may call it to our attention.

Mr. WALKER. Thank you very much. That is all the questions that I have, Mr. Chairman.

Mr. WEISS. Thank you, Mr. Walker.

Dr. Crawford, last July, CVM's Cancer Assessment Committee [CAC] unanimously concluded that albendazole, a drug used in cattle and sheep, induced malignant tumors in animals.

[The memorandum of the CAC's meetings and findings, and related documents follow:]

– J. Hauswirth

MEMORANDUM OF CONFERENCE
July 2, 1984 & July 26, 1984

Place: Center for Veterinary Medicine/Human Food Safety, Conference Room, Parklawn Bldg., Rockville MD 20857

Purpose: Meeting of the Cancer Assessment Committee

Participants:

CAC Members

Dr. T.M. Farber, Chairman, Division of Toxicology, HFV-330 T.M. Farber
Dr. R.C. Livingston, Division of Chemistry, HFV-340 for RCL
*Dr. R. Condon, Biometrics Group, HFV-124 Robert J. Condon
Dr. R. Furrow, Deputy Director Division of Veterinary Research, HFV-501 for RD Furrow
Dr. B.R. Sonawane, Executive Secretary, Division of Toxicology, HFV-330 B.R. Sonawane

*Dr. Condon represented Dr. J. Colaianne who is a member of the CAC.

Others

Dr. J.W. Hauswirth, Division of Toxicology, HFV-330
Dr. R.B. Benson, Consumer Safety Staff, HFV-320
Dr. S. Fitzpatrick, Consumer Safety Staff, HFV-320

Subject: Albendazole

The meeting of the Cancer Assessment Committee of the Center for Veterinary Medicine was held on July 26, 1984 to discuss the toxicology of albendazole. This final CAC meeting on albendazole toxicology was a follow-up to the conference held at FDA on June 20, 1984 between the CVM staff, the sponsor's representatives and their consultants; as well as the CAC meeting held on July 2, 1984. The following summary of these conferences reflect the positions of the sponsor, and the CVM/CAC's scientific deliberations and recommendations.

June 20, 1984 Meeting Between The Sponsor's Representatives and The CVM Staff:

The purpose of this meeting was to discuss the biological significance and statistical considerations relative to the occurrence of histiocytic sarcoma seen in the albendazole life-time rat study. Dr. Theodorides (SKF) presented an overview and summary of the data relative to the occurrence of histiocytic sarcoma in the life-time albendazole rat study. The major emphasis of his presentation was that the histiocytic sarcomas observed in the albendazole rat study were the result of a fortuitous phenomenon and were not compound related. Dr. Theodorides argued that this conclusion was based on some of the following biological and pathological considerations pertinent to the evaluation of toxicology of albendazole:

1. The mouse, according to FDA's letter of November 14, 1983 "has been found to be acceptable and shows that albendazole is not carcinogenic to CD_1 mice".

2. Histiocytic sarcoma is not a new tumor. This tumor has been reported in untreated rats for many years and has been described by various terminologies.

3. There is no clear dose response relationship for the incidence of histiocytic sarcoma in the low- and mid-dose groups and it is similar to that of the controls. The increased incidence of histiocytic sarcoma in the high-dose males is statistically significant when compared with control group I but not when compared with control Group II; the same is true with the females.

Dr. Theodorides presented the data on the incidence of histiocytic sarcoma in male as well as female rats, the observed incidences for control groups from the historical records of Bio/dynamics, the observed incidences of histiocytic sarcoma in rats from the Newberne experiment with sodium nitrite (Dr. Squire's data), and a summary of worldwide albendazole usage.

He concluded that consulting pathologists (retained by the firm) and their consulting biostatistician (Dr. Carlborg) were in agreement that the incidence of histiocytic sarcoma in the high-dose male rats is a fortuitous event because a similar tumor incidence has been observed in some Bio/dynamics historical controls and in the Newberne Nitrite Study, and therefore, the histiocytic sarcoma findings in the albendazole study are not compound-related.

Dr. Carlborg presented the statistical evaluation of the data independent of the analysis conducted by the SmithKline's statisticians. He summarized his findings and conclusions for the CVM representatives (submitted by the sponsor under the cover letter dated June 25, 1984). Carlborg's statistical evaluation of the results by the Fisher's Exact Test for the male rats indicated a significant ($P<0.01$) increase in the tumor incidence rate in the high-dosage group when compared with the pooled controls. He interpreted the results indicating a very small probability ($P = 0.0085$) that the observed increase in tumor incidence at the high dose was due to a chance alone (a false positive). Dr. Carlborg indicated that for the comparison of the high-dose versus the pooled control had a p-value of 0.027 which is not as significant as for female rats.

Dr. Carlborg raised a longstanding concern about the potentially high "false positive" rate associated with long-term bioassay studies, involving two rodent species, two sexes, and many tissue sites. He aruged that in the rat and the mouse studies such as conducted with albendazole there are approximately 400 endpoints (i.e. variables) for statistical analyses.

Consequently, if each endpoint is subjected to a 0.05 significance rule one would expect a large number of significant results due to chance alone. Dr. Carlborg questioned the validity of running linear trend tests in chronic bioassay studies when cell frequencies are less than 3 and argued against Peto analysis of data. Dr. Carlborg also suggested that the "false positive" rate in long-term rodent bioassay studies is so high that only extremely statistically significant findings should be considered reliable.

Dr. Boreje (Bio/dynamics, Inc.) stated that the incidence of histiocytic sarcoma varies considerably amongst groups of rats and is very variable from one experiment to another. The incidence of this tumor in the albendazole study is within the range of this variability and, therefore, not compound related. Dr. Boreje noted that previous to Dr. Squire's description of this tumor as a new entity in the rat, Bio/dynamics as well as other laboratories had used several other terms to describe this tumor. Drs. Goodman and Goldschmidt (the firm's consulting pathologists) agreed with Dr. Boreje's interpretation and diagnosis of histiocytic sarcoma. They also emphasized the importance of the use of historical controls in evaluating the biological significance of tumors seen in the carciougenicity studies with albendazole.

Dr. Squire (the sponosor's consulting pathologist) commented that he had read selected slides from the albendazole study and, likewise, agreed with the interpretations of others (Drs. Goodman, Boreje and Goldschmidt). He also stated that the range of variability of histiocytic sarcoma occurrence is high, therefore, the incidence observed in the albendazole study was not surprising and is consistent with the normal background incidence of this tumor. He concluded that based on his experience that the tumor occurrence was not related to the administration of albendazole.

Dr. Farber requested Dr. Carlborg to present his statistical agruments in writing. He raised the question whether it is scientifically sound to compare the Bio/dynamics data with Dr. Newberne's study given that the incidence of common spontaneous lesions may vary between laboratories. Dr. Goodman responded that the source (Charles River Laboratories, Inc.) and the strain of rats (Sprague-Dawley, CD strain) were the same. She also emphasized that in the albendazole study a number of pathologists have reviewed the slides and all have agreed with their original diagnosis but there is some inter-laboratory variability resulting from different diagnoses.

Dr. Colaianne questioned Dr. Carlborg's statistical interpretation of the data, especially related to the argument of "false positive" findings and the pooling of sexes for data analysis. Dr. Colaianne also questioned Dr. Carlborg's arguments for not using Peto analysis based on the survivability data.

Dr. Settepani noted that he personally had some difficulty with the use of historical control data and the terminologies used to describe the incidence of histiocytic tumors in albendazole study. The sponsor's pathologist reiterated their arguments as stated earlier.

Dr. Farber concluded the meeting noting that the information presented was very useful and would be considered for the CAC decision concerning the albendazole studies.

July 2, 1984; The Cancer Assessment Committee Meeting

The purpose of this meeting was to discuss the sponsor's submission dated June 25, 1984 summarizing their presentations and arguments made at the June 20, 1984 conference with the CVM staff. All the members of the Cancer Assessment Committee were present. In addition, Drs. Hauswirth, Benson and Fitzpatrick also participated in the discussions.

The major thrust of the discussion was concentrated on the sponsor's arguments (the firm's consulting pathologists and statisticians) that the incidence of the histiocytic sarcomas observed in the albendazole chronic bioassay study in rats is a false positive finding and the additional statistical support obviates the need for a Peto analysis of the data.

Dr. Furrow was in agreement with the sponsor's pathologists with respect to the nomenclatures used in description of tumors, and the evaluation criteria applied for the histiocytic sarcoma in the albendazole study. He noted that the historical control data submitted by the sponsor's contractor (Bio/dynamics, Inc.) may have included all related categories of tumor types and even if one reclassifies these tumors, the overall indicence of tumors would not significantly change.

Dr. Sonawane introduced a literature reference (Graves, P. and Faccini, J.M.: Brit. J. Cancer 43:402-411, 1981) on spontaneous fibrous histiocytic neoplasms in rats for Dr. Furrow's review since those authors claimed the spontaneous incidence of the tumor types apparently similar to the new entity described by Dr. Squire is low (2.7%). Dr. Furrow commented that the criteria used for the classification by the European authors is different and the tumor types are not the same as described by Dr. Squire, therefore, we should not consider the publication in question for the evaluation of the albendazole study.

Dr. Colaianne questioned the use of Dr. Newberne's nitrite study control data as background information because the study was not designed to look for histiocytic sarcoma, and a great degree of variability exists in the incidence of tumors reported. Dr. Colaianne argued against Dr. Carlborg's theoretical calculations regarding the potential for false positives using 400 endpoints when the actual number of possible endpoints could be less than 40 to express a false positive response.

Dr. Farber requested Dr. Colaianne to conduct a statistical evaluation of the incidence of histiocytic sarcomas in the albendazole chronic rat study and to explore the possiblity whether multiple statistical comparisons such as a Bonferoni correction could be used to adjust the critical p-value.

Dr. Hauswirth raised the issue of the incidence rates of endometrial polyps among females in both the chronic rat and the chronic mouse studies with albendazole. She asked Dr. Furrow whether endometrial polyps could be grouped with endometrial sarcomas for conducting a prevalence analysis of the data. Dr. Furrow responded that it is very appropriate to do so. The appropriateness of combining endometrial polyps with sarcomas was further confirmed by telephone conversations by Dr. Hauswirth with Dr. Lorentzen (Center for Food Safety and Applied Nutrition) and with Dr. Ward (National Cancer Institute). Dr. Farber terminated the meeting by concluding that the Committee will make final scientific deliberations and recommendations after the statistical interpretation of the issues raised are satisfactorily resolved.

July 26, 1984, The Cancer Assessment Committee Meeting

The purpose of this final CAC meeting on albendazole toxicology was to make scientific deliberations and recommendations with respect to the issues raised so far by the CVM staff and to consider the sponsor's arguments.

Dr. Farber requested Dr. Condon to present statistical evaluation of the histiocytic sarcoma incidence in rats fed albendazole in a chronic carcinogenicity study (Biometrics Group - HFV-124 memorandum dated July 17, 1984). Dr. Condon summarized the statistical evaluation of histiocytic sarcoma incidence in rats as well as the endometrial polyps plus sarcomas in rats and mice fed albendazole. The following conclusions as stated in HFV-124 memorandum dated July 17, 1984 are included here as a part of the record, for details please see the text of the review as outlined in the same memorandum.

1. The results of Dr. Carlborg's statistical analyses of the histiocytic sarcoma data indicate that there was a statistically significant (p= .0040) positive dose-response trend associated with tumor incidence in the male rat. The finding was further confirmed by the significance obtained with the Fisher's Exact Test (p= .0085) comparison of the high dose incidence versus the pooled concurrent control.

2. The results for the female rat strongly support those obtained for the male. Again Carlborg's analyses indicate a significant linear trend (P= .0012) in the females, and while it is recognized that due to the spacing of the doses this trend test essentially amounts to a comparison of the control versus the high dose group, the results of the Fisher's Exact Test also suggest that a statistically significant (p= .027) increase in tumor incidence occurred at the high dose level.

3. Although the above results are fairly conclusive, based on the recommendations of the IARC Committee (1980) an analyses of the data using the more sensitive survival adjusted analysis suggested by Peto et al (1980) were performed. Since there was some question as to whether histiocytic sarcoma should be considered "incidental" or "fatal" the analyses were run under both assumptions. The results were essentially the same for both analyses and very similar to those of Carlborg's. The linear trends were highly significant for both males (incidental p=.0047, fatal p=.0016) and females (incidental p=.0012,

fatal p=.0010). Likewise, the comparisons of the high dose incidence versus the control were also significant for both males (incidental p=.0036, fatal p=.0021) and females (incidental p=.012, fatal p=.013). As would be expected the combined results for the two sexes were even more statistically significant than for each sex alone (linear trend tests, incidental p=.00005, fatal p=.00001; control vs high dose, incidental p=.00023, fatal p=.00014).

4. In addition to the evaluation of the histiocytic sarcoma data in rats, a request was made for a statistical analysis of the incidence rates of endometrial polyps and sarcomas alone and combined among females in both the chronic rat and chronic mice studies. Because of the absence of full life table data analyses were limited to simple Armitage linear trend tests and Fisher's Exact Tests. The results of these analyses indicate a statistically significant positive dose response trend in both rats and mice. (See attached Table 4 and 7 from HFV-124 memorandum dated August 1, 1984).

5. A number of other issues raised by Dr. Carlborg's presentation are addressed in HFV-124 memroandum dated July 17, 1984. In particular Carlborg suggests that the "false positive" rate in long-term rodent bioassay studies is so high that only extremely statistically significant findings should be considered reliable. A number of very prominent authorities in the field have thoroughly refuted this concern and have pointed out that the true false positive rate in such bioassay studies is nominal. Fears et al (1977), Gart et al (1979), Mantel (1980), and Haseman (1983). For details see the text and references included in the review.

6. With respect to Bonferroni adjustments for multiple dose comparisons there is still considerable controversy over the validity of these adjustments in long-term bioassay evaluations. Dr. Carlborg uses them when he divides the normal significance levels by 3 to adjust for the 3 possible comparisons of dosed groups to control. In the case of a significance level of 0.05 this gave him .05/3 = .017 as the critical significance level. However, Mantel (1980) among others, has pointed out the potential abuse associated with these adjustments. If the dosage levels spacing is not clearly defined, the way it is in the NTP studies where the dose levels are chosen to be specific fractions of the maximum tolerated dose, then it is possible to manipulate the required significance level and make it as small as desired, simply by including a large number of low dose groups below the minimum detectable response level. Moreover, there are very serious questions about the appropriateness of adjusting for the multiple comparison of each dose level with the control when we know a priori that the control versus high dose comparison is the critical comparison in the types of chronic carcinogenicity studies reviewed by FDA.

7. With respect to the historical control data, most authors agree (Peto, 1980; Mantel, 1980; Haseman, 1983) that historical data must be used very carefully since the conditions under which it was collected may

not be representative of the conditions under which the current bioassay study was run. Generally, the data is limited to historical rates obtained in the same laboratory where the long-term bioassay was conducted. We agree with Dr. Carlborg that such data should not be used in any actual statistical testing procedure, but should be viewed as background information regarding the general spontaneous rate experienced with a particular tumor type at a particular tissue site. The Bio/dynamics data was collected in the same laboratory where the albendazole study was run. The average indicence rates (.0265 for male rats, .0280 for female rats) are consistent with the pooled concurrent control rates observed in the study (.0181 for males, 0.0230 for females). The historical control data submitted by the Bio/dynamics represented 14 different studies and the observed incidence of claimed histiocytic sarcomas (or several other terms used) was highly variable (0% to 9.2%). The Committee questioned the validity of the data in evaluation of the albendazole studies because those slides were not reexamined for the accuracy of diagnosis. The historical control data from the Newberne sodium nitrite study is more questionable since it was obtained from another laboratory under different conditions. It should probably be viewed as very crude background information on the spontaneous rate associated with histiocytic sarcomas and the estimates of the rates should be limited to those calculated from the dedicated controls (.030 for males, .045 for females).

It is tempting here to establish a rigid statistical decision rule for stating that some observed tumor increase is statistically significant and consequently biologically believable. Some authors, such as Peto et al (1980) have suggested that it might be advisable to require the p-value for a single isolated event to be smaller than .01 before declaring an observed increase significant by the Fisher's Exact Test. However, they are quick to point out that this rule is not applicable when the tumor is very rare or when there is supportive evidence of a significant increase in the other sex or another strain or species. Such supportive evidence was obtained for both the histiocytic sarcoma and the endometrial polyps in the present study. Consequently, in the final evaluation of the results of a chronic carcinogenicity study, the statistical p-values for various comparisons are very informative, but the decision as to whether the observed results are adequate to consider the test compound "safe" for human exposure is a biological decision.

The Committee discussed each of the points as outlined above and was in agreement with Dr. Condon's interpretation of the data. Dr. Condon pointed out that since the question remains whether histiocytic sarcomas were fatal tumors (cause of death) or were incidental tumors (not a primary cause of death), he further analyzed the data by using the exact date of death as provided by Dr. Heuswirth rather than at 6 months intervals as has been done in July 17, 1984 memorandum. The data on histiocytic sarcoma in rats and endometiral polyps and sarcomas in both mice and rats have also been reanalyzed incorporating the exact date of death rather than treatment summaries as used in July 17, 1984 memorandum. (See attached Tables 4 and

7 from HFV-124 memorandum dated August 1, 1984). Dr. Condon concluded that the statistical reanalysis (prevalence analysis) of data indicated that feeding of albendazole is associated with an increase in histiocytic sarcomas in both male and female rats and an increase in endometrial polyps and sarcomas in both mice and rats. The repeatability (both sexes or both species) of these increases and the associated low probability values virtually eliminate the possibility of the occurence of false positive results.

The Committee also had some discussion about the Sprague-Dawley (CD strain) rats being susceptible to environmental changes. The Committee thought the historical control data on spontaneous incidence of histiocytic sarcoma and the different nomenclature used to describe the tumor type as presented by the sponsor's contractor (Bio/dynamics) were not relevant to the evaluation of albendazole rat bioassay. The sponsor's contractor (Bio/dynamics) probably never reexamined the slides to demonstrate that the tumors in question were the same or the criteria used for the evaluation of these tumors by different pathologists over a period of time did not change. The Committee also considered the argument of the sponsor for using the historical control data from the Newberne's sodium nitrite study but rejected it because it was obtained from another laboratory under different environmental conditions, and markedly different diet. The Committee concluded that the historical control data of Bio/dynamics as well as that of the Newberne nitrite study in rats is of a tertiary nature, therefore, is of little relevance and could not materially influence the Bio/dynamics evaluation of albendazole chronic rat bioassay. The Committee agreed that the most appropriate (and important) comparison of an experimental group is with its concurrent controls (matched controls).

Finally, the Committee concluded that feeding of albendazole caused statistically significant increases in histiocytic sarcomas in both male and female rats as well as increased combined incidence of endometrial polyps and sarcomas in both mice and rats. The increased incidence (biologically and statistically) of these two types of tumors (both sexes or both species) indicate that albendazole is oncogenic to rats (Sprague Dawley, DC strain) and to mice (CD-1).

B.R. Sonawane, Ph.D.

cc: HFV-16(2)
HFV-100
HFV-301
HFV-320(2)
HFV-330
HFV-340
t/d:08-04-84:tlc:BRSonawane
t/f:08-09-84:tlc:BRSonawane

TABLE 4. Probability Values for Histiocytic Sarcomas Using Exact Day of Death

	Overall X^2 Test	Linear Trend	Control vs High Dose
I. Prevalence Analysis[a]			
Males	.071675	.005345	.002257
Females	.026873	.004425	.027963
Combined	.003753	.000138	.000368
II. Fatal Tumor Analysis[b]			
Males	.010620	.000454	.000275
Females	.007510	.001447	.011629
Combined	.000126	.000004	.000029

[a] Histiocytic Sarcoma assumed not to be cause of death

[b] Histiocytic Sarcoma assumed to be cause of death

TABLE 7. Probability Values from Prevalence Analysis of Endomentrial Polyps and Sarcomas[a]

Data Set	Overall X^2 Test	Linear Trend	Control High Dose
Mouse	.1877	.0252	.0297
Rat	.1347	.0093	.0096
Combined	.0194	.0011	.0013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Date August 1, 1984

From Biometrics Group, HFV-124

Subject Statistical Evaluation of Histiocytic Sarcoma Incidence in Rats and Endometrial Polyps Plus Sarcomas in Rats and Mice Fed Albendazole

To Toxicology Staff, HFV-330
ATTN: Dr. Judith W. Hauswirth

NADA 110-048

The data on the incidence of histiocytic sarcomas in male and female rats have been reanalyzed using the exact date of death for these rats rather than 6 month intervals used in the 7/17/84 memo. Because there remains some uncertainity as to whether histiocytic sarcomas are fatal tumors (death of animal was caused by the tumor) or are incidental tumor (death of animal not caused by the tumor), the data have been analyzed by both fatal tumor and prevalence methods. It should be noted that the statistical analysis for fatal tumors will result in smaller probability values than the statistical analysis of incidental tumors (prevalence analysis). If the true situation is that histiocytic sarcomas were fatal for some but not all animals, the correct probability values would be somewhere between the limits set by the fatal tumor analysis and the prevalence analysis.*

The histiocytic sarcoma data used for the prevalence analysis are given in Table 1 and the data used for the fatal tumor analysis are given in Tables 2 (males) and 3 (females). The results of these statistical analyses are given in Table 4.

The data on endometrial polyps and sarcomas in both mice and rats have also been reanalyzed incorporating the exact date of death rather than treatment summaries as used in the 7/17/84 memo. The endometrial polyps and sarcomas have been considered incidental tumors and a prevalence analysis has been used.

The data used for the analysis of endometrial polyps and sarcomas are given in Table 5 for mice and Table 6 for rats. The results of are given in Table 7.

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* Histiocytic sarcomas would appear to be in the fatal class because the rate in the animals sacrificed at the end of the study was low (males) or zero (females).

Conclusion:

These data indicate that the feeding of albendazole is associated with an increase in histiocytic sarcomas in both male and female rats and an increase in endometrial polyps and sarcomas in both mice and rats. The repeatability (both sexes or both species) of these increases and the associated low probability values virtually eliminate the possibility of the occurrence of false positive results. Tables 4 and 7 should be used to update Tables A and B of the 7/17/84 memo.

Robert J. Condon

Robert J. Condon, Ph.D.
Mathematical Statistician

cc: Dup
HFV-330
HFV-320
HFV-124
HFV-16(2)
Dr. Colaianne
Dr. Settepani
RJCondon,HFV-124/sb/8/1/84

TABLE 1. Data Used for Prevalence Analysis of Rat Histiocytic Sarcomas

Time	Prevalence of Histiocytic Sarcomas				
	Control	Low Dose	Mid Dose	High Dose	Total (Rate)
Males					
0-430	0/20	0/7	0/13	0/8	0/48 (0.0)
433-551	0/5	0/8	1/8	0/7	1/28 (.036)
552-735	1/41	1/24	0/18	3/32	5/115 (.043)
737-788	0/20	1/5	0/11	1/7	2/43 (.047)
789-831	0/19	0/10	2/9	1/12	3/50 (.060)
833-840	0/4	1/3	1/4	0/1	2/12 (.167)
841-846	0/6	1/1	0/0	1/4	2/11 (.182)
Termination	2/65	0/32	0/27	2/19	4/143 (.028)
Females					
0-521	0/15	0/3	0/7	0/12	0/37 (0.0)
522-575	1/12	0/8	0/3	0/4	1/27 (.037)
581-769	1/62	0/23	2/30	3/31	6/146 (.041)
770-843	2/29	0/17	0/14	2/12	4/72 (.056)
844-848	0/3	0/2	0/1	1/3	1/9 (.111)
849-850	0/0	0/1	0/0	1/1	1/2 (.500)
Termination	0/58	0/36	0/34	0/27	0/155 (0.0)

TABLE 2. Data Used for Fatal Tumor Analysis of Histiocytic Sarcomas in Male Rats

	Tumor/Number of Animals at Risk			
Day	**Control**	**Low**	**Mid**	**High**
433	0/160	0/83	1/77	0/82
552	0/155	0/75	0/69	1/75
565	0/154	0/74	0/67	1/74
587	1/154	0/73	0/65	0/70
622	0/145	0/69	0/63	1/65
648	0/143	1/66	0/51	0/61
737	0/114	1/51	0/48	0/43
750	0/108	0/47	1/40	1/41
789	0/94	0/46	1/36	0/36
798	0/90	0/42	0/33	0/33
813	0/83	0/39	0/32	1/30
833	0/75	1/36	1/30	0/24
837	0/73	0/35	0/27	0/24
841	0/71	1/33	0/27	0/23
842	0/70	0/32	0/27	1/23
Termination	2/65	0/32	0/27	2/19

TABLE 3. Data Used for Fatal Tumor Analysis of Histiocytic Sarcomas in Female Rats

	Tumor/Number of Animals at Risk			
Day	Control	Low	Mid	High
522	1/164	0/87	0/82	0/78
581	0/152	0/79	1/79	0/74
625	0/148	0/76	1/72	0/71
631	0/147	0/74	0/70	1/70
652	0/145	0/70	0/69	1/68
717	0/122	0/61	0/57	1/56
737	1/107	0/57	0/54	0/49
770	0/90	0/56	0/49	1/43
776	1/88	0/54	0/48	0/42
779	1/86	0/51	0/46	0/42
806	0/79	0/47	0/44	1/37
844	0/74	0/39	0/35	1/31
849	0/61	0/37	0/34	1/28
Termination	0/58	0/36	0/34	0/27

TABLE 4. Probability Values for Histiocytic Sarcomas Using Exact Day of Death

I. Prevalence Analysis[a]	Overall X^2 Test	Linear Trend	Control vs High Dose
Males	.071675	.005345	.002257
Females	.026873	.004425	.027963
Combined	.003753	.000138	.000368
II. Fatal Tumor Analysis[b]			
Males	.010620	.000454	.000275
Females	.007510	.001447	.011629
Combined	.000126	.000004	.000029

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[a] Histiocytic Sarcoma assumed not to be cause of death

[b] Histiocytic Sarcoma assumed to be cause of death

TABLE 5. Data Used for Prevalence Analysis of Mouse Endometrial Polyps and Sarcomas

Time	Control	Low	Mid	High	Total (Rate)
0-427	0/21	0/13	0/9	0/20	0/63 (0.0)
431-540	0/19	0/5	2/12	0/8	2/44 (.045)
547-709	3/55	1/20	1/25	3/26	9/126 (.071)
710-755	1/17	1/11	0/9	3/11	5/48 (.104)
Termination	4/87	4/51	6/45	3/35	17/218 (.078)

TABLE 6. Data Used for Prevalence Analysis of Rat Endometrial Polyps and Sarcomas

Time	Control	Low	Mid	High	Total (Rate)
0-502	0/15	0/3	0/6	0/11	0/36 (0.0)
503-627	0/16	0/13	1/12	0/6	1/47 (.021)
628-819	2/74	2/28	2/35	3/30	9/167 (.054)
820-850	0/16	2/10	0/2	0/8	2/36 (.056)
Termination	6/58	4/36	5/34	7/26	22/154 (.143)
Sacrifice	3/20	0/10	1/10	2/10	6/50 (.120)

TABLE 7. Probability Values from Prevalence Analysis

of Endomentrial Polyps and Sarcomas[a]

Data Set	Overall X^2 Test	Linear Trend	Control High Dose
Mouse	.1877	.0252	.0297
Rat	.1347	.0093	.0096
Combined	.0194	.0011	.0013

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[a] These values are different from those in the memo of 7/17/84 because the exact day of death for each animal has been used instead of deaths during 6 month intervals.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Date August 8, 1984

From Biometrics Group, HFV-124

Subject Calculation of Acceptable Tissue Residue Levels for Albendazole Based on Tumors Observed in the Chronic Feeding Studies

To Toxicology Staff, HFV-330
ATTN: Dr. Judith W. Hauswirth

NADA 110-048

The attached table lists the "SOM" calculations for albendazole. These calculations are based on histiocytic sarcomas in male and female rats and endometrial polyps plus sarcomas in both mice and rats. The most sensitive subgroup, in this case endometrial polyps plus sarcomas in rats, is generally used to obtain the amount of total residues that would need to be monitored. Therefore, the acceptable levels of total residues in tissues would be 13.2 ppb for muscle, 26.4 ppb for liver, and 39.6 ppb for kidney.

Robert J. Condon
Robert J. Condon, Ph.D.
Mathematical Statistician

cc: HFV-330
HFV-320
HFV-124
HFV-16(2)
DR.Colaianne
Dr.Settepani
Dr.Norcross
RJCondon,HFV-124/8/8/84

Calculation of Acceptable Tissue Levels for Albendazole
Residue Based on Chronic Feeding Studies

	Histiocytic Sarcoma (Rats)			Endometrial Polyps + Sarcomas	
Calculation	Males	Females	Combined	Mice	Rats
			ug/kg		
Level causing increased risk over background of 1 in 1 million (ug/kg)	.13	.28	.19	.13	.11*
			ug		
Acceptable amount for 60 kg person (ug)	7.8	16.8	11.4	7.8	6.6
			ppb		
Acceptable Level for total diet of 60 kg person assuming 1500 g intake (ppb)	5.2	11.2	7.6	5.2	4.4
Acceptable tissue Levels for edible tissues-after adjustment for consumption (ppb)					
			ppb		
Muscle	15.6	33.6	22.8	15.6	13.2
Liver	31.2	67.2	45.6	31.2	26.4
Kidney	46.8	100.8	68.4	46.8	39.6

*The lowest of these levels should be used for calculation of acceptable tissue levels

Mr. WEISS. Concerned about the safety of meat from albendazole-treated animals, FDA advised the drug's sponsor, SmithKline Animal Health Products, that the drug would have to be removed from the market. Was albendazole removed from the market?

Dr. CRAWFORD. Yes, Mr. Chairman.

Mr. WEISS. In 1979, FDA regarded albendazole as a suspect carcinogen that could not be approved for marketing unless animal carcinogenicity studies were done. Nonetheless, on October 1, 1979, FDA advised the sponsor that it could distribute albendazole under an emergency investigational new animal drug [INAD] exemption, to combat an outbreak of liver flukes in cattle and sheep in four States.

[FDA's October 1, 1979, letter to the sponsor follows:]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

OCT 01 1979

Mr. George Ebright
Smith Kline Animal Health Products
1600 Paoli Pike
West Chester, Pennsylvania 19380

Dear Mr. Ebright:

This letter is in response to your May 18, 1979, amendment to your pending New Animal Drug Application (NADA 110-048) and confirms our telephone conversations of September 7 and 10, 1979.

Because of the acute problem with liver flukes in cattle—particularly in the Southeast and Texas—and the lack of suitable drugs for treating this condition, we have given very careful consideration to your request for a limited approval of albendazole.

As you were advised by phone, the data available in your NADA are not now sufficient to approve the drug. In particular, there were no chronic toxicity data, and the depletion studies were not sufficiently reliable to make an accurate determination of the withdrawal period. Our concerns about the safety of albendazole, including its potential carcinogenicity, are substantial.

We recognize that there are serious problems in Texas and Florida with liver fluke disease, which, if not relieved, may result in serious disruption to the cattle industry in those states. We are interested in bringing some relief to these cattle producers and the affected animals. However, given the concerns over the safety of albendazole, the Agency can approve it for restricted and temporary use in the current emergency only after receiving reasonable assurance that virtually no residues of the drug would find their way into the food supply.

As I have informed you, we would be willing to grant limited, temporary use of the drug under an INAD this fall. The procedure under 21 CFR 511.1 should be used as a guide for setting up such a program. The procedure which we are suggesting for this limited use of albendazole is based on a number of factors:

Mr. George Ebright

1. Limited depletion data are required in order to arrive at a probable level of 2 ppb in liver at 150 days. (We propose labeling which includes 180-day withdrawal.)

2. We believe that it is reasonable to expect that the type of cattle receiving the drug (e.g. brood cows) will not ordinarily become food. (Some method of identification of treated animals would be required.)

3. During the fall and spring round-ups, cattle being "culled" to go to slaughter will not ordinarily be dosed with flukacide (i.e., there is no advantage to treating them, and the cost of the medication will also be a deterrent).

4. Subchronic studies with albendazole indicate a safe level of 100 ppb, carcinogenicity questions aside.

5. Smith Kline must be willing to undertake immediately additional depletion studies using more cattle to provide data points nearer the suggested withdrawal period.

6. We must rely on considerable assistance by USDA or state disease control officials in monitoring the use of the drug.

We particularly stress the importance of prompt submission of accurate withdrawal information. The withdrawal period of 150 days was determined from an estimated 14 day half-life for the depletion of albendazole residues. This was intended solely to allow limited investigational studies and not for widespread use of the drug. The determination was based on a single value in a single animal at day 40 post medication, at which time the total residues in liver were 340 ppb, approximately 170 times higher than the 2ppb level considered safe by threshold assessment.

The following data are required for a formal NADA approval of albendazole (solely for treating cattle for flukes): At least 3 points and 3 animals per point (9 animals) would be necessary for an extrapolation to be reliable for determining the depletion time to the 2 ppb level. The data must include a depletion point at or near the tolerance and should be submitted no later than 6 months from now. On the basis of these studies, assuming they affirmed the current depletion projections, the Agency could determine with confidence an accurate withdrawal period sufficient to ensure safety and provide the basis for NADA approval of the drug for use in brood cattle for liver flukes. Such an approval would be contingent on your continued commitment to timely completion of chronic toxicology studies and would be revoked if those studies demonstrated carcinogenicity.

Mr. George Ebright

Again, I must emphasize that this procedure for allowing limited availability of the drug is offered as a means of dealing with the critical emergency, i.e., liver fluke infestation in cattle. Approval for nationwide marketing for uses in addition to treatment of liver fluke infestation is contingent on receipt of data which respond to the traditional food safety requirements. If you have any questions as to the precise needs, your representative should contact Dr. William Price, Branch Chief, Metabolic Branch, Division of Drugs for Ruminant Species, Bureau of Veterinary Medicine.

Sincerely yours,

Sherwin Gardner
Acting Commissioner of Food and Drugs

cc: NADA Orig., Dup., Trip.
HFF-1
HFF-6, Scheuplein
HFF-140
HFF-148
HFF-152
HFF-180
HFR-3100
HFV-1
HFV-100
HFV-120
HFV-9
HFV-200
HF-1, HF-2
HFJ-5
HFJ-20
HFA-224
drafted:RJScheuplein:mtd:9/13/79:hvb:9/19/79
Init: RJScheuplein:9/18/79
DGuest:9/19/79
LCrawford:9/19/79
Edit:JDoherty:9/20/79
SMPape:9/21/79
SGardner:9/21/79
f/t:mbr:9/26/79

Mr. **Weiss**. Dr. Crawford, what provision in the Food, Drug, and Cosmetic Act authorizes FDA to permit the emergency use of a new animal drug that has not been approved as safe and effective for its intended purposes?

Dr. **Crawford**. Mr. Chairman, at this point, may I confer for just a moment with counsel?

Mr. **Weiss**. Of course.

[Pause.]

Dr. **Crawford**. Is it all right if Mr. Drozen comes up?

Mr. **Weiss**. Absolutely. In fact, if you could find a chair to pull up next to Dr. Crawford, Dr. Drozen——

Mr. **Drozen**. Mr. Drozen.

Mr. **Weiss**. Mr. Drozen. You call me a judge, and I will call you a doctor. You are still under oath from yesterday.

Mr. **Drozen**. Could I just make one brief introductory statement?

Mr. **Weiss**. Of course.

Mr. **Drozen**. And that is, as I mentioned yesterday, I am a staff attorney at the Food and Drug Administration. I should have mentioned it yesterday. That the opinions that I offer are my opinions, and not necessarily the opinions of the Office of General Counsel at FDA, or of course the opinions of the agency.

So I am offering my personal opinion as to at this point the statutory interpretation. I have no specific familiarity with the approval process or what happened with albendazole. I can only offer my opinion as to what may have happened.

Mr. **Weiss**. That is all right. But I would ask that if, upon leaving the hearing and consulting with the Office of General Counsel, you find that your personal opinion is at variance with that of the Office of General Counsel, that you advise us of this in a submission for the record. We want the record to be as accurate as possible.

Mr. **Drozen**. I will do my best, Mr. Chairman, to do that.

[Mr. Drozen subsequently advised the subcommittee: "I am not aware of any attorney in the Office of the General Counsel whose opinion is at variance with mine."]

Mr. **Weiss**. Thank you.

Now the question is: What provision in the Food, Drug, and Cosmetic Act authorizes FDA to permit the emergency use of a new animal drug that has not been approved as safe and effective for its intended purposes?

Mr. **Drozen**. Again, Mr. Chairman, I have not reviewed the documents involved with albendazole. My assumption from a legal standpoint in terms of the provisions FDA uses to permit the investigational new animal drug use of a new animal drug is section 512[j] of the act, which permits exemption for drugs intended for investigational use.

The language that you are talking about as far as emergency use is not found specifically in that exempting provision.

Mr. **Weiss**. As a matter of fact, Dr. Crawford, in a September 6, 1979, letter regarding albendazole, you wrote that there is "no provision in our law for emergency uses" of unapproved new drugs.

[The letter referred to follows:]

SEP 6 1979

Don E. Bailey, DVM
Secretary-treasurer
American Association of Sheep
and Goat Practitioners
248 N. W. Garden Valley Road
Roseburg, Oregon 97470

Dear Dr. Bailey:

This letter is in response to your August 22, 1979, letter to me and a follow up of our discussion at the meeting in Salt Lake City concerning the serious liver fluke problem. We are aware, of course, of the dilemma facing sheep, goat, and cattle producers in Oregon, and in fact, several areas throughout the United States.

As you point out in your letter Coriban, Flukanide, and Albendazole is being used by sheep and cattle raisers in other countries. You are perhaps also aware that we have no record of a pending New Animal Drug Application (NADA) for a product for treatment of liver fluke infestation in sheep, and goats. That is to say, it appears that no drug sponsor is petitioning the Food and Drug Administration for a drug for use in sheep and goats. While an application has not been submitted for Coriban (diamphenethide) or Flukanide (rafoxanide), we do have before us a pending NADA for use of albendazole in cattle. With this the case and with no provision in our law for emergency uses of drugs, the question of liver fluke control in sheep is particularly vexing. As a start, from your end, The Association of Sheep and Goat Practitioners may wish to initiate some activity with appropriate drug sponsors in order to make drugs of this type available to sheep and goat practitioners and producers.

We know this matter is vitally important particularly at this time of the year and I can assure you that we are actively exploring the options we have under the Federal Food, Drug, and Cosmetic Act in order to find a solution to the liver fluke problem. You realize, of course, that any plan or course of action decided upon must assure the health of the public as well as adequately satisfy the legal aspects involved. I am hopeful that we will be able to quickly work through these aspects of the issue so that we can find a means of bringing relief to the animals and to the livestock producer.

Thank you for sending us the paper published in the American Society of Parasitologists, your article of the proceeding of the 1978 U.S. Animal Health meeting held in New York, and we have noted the Merck Manual item regarding fluke remedies.

I appreciate very much your thoughtful description of the situation in Oregon. Please be assured that I am doing everything possible to quickly resolve the problem you have described.

Sincerely yours,

Lester M. Crawford, DVM

Lester M. Crawford, D.V.M.
Director, Bureau of
Veterinary Medicine

Mr. **Weiss**. Do you recollect that letter, or should I show it to you?

Dr. **Crawford**. Yes, I recollect the deliberations leading up to this emergency use, and that was one of the points that we raised.

Mr. **Weiss**. That there is no such provision in the law?

Dr. **Crawford**. We wondered if there was not. And at that time, the conclusion was that it ought to be explored much further. And that is the substance of the letter, as I recall it.

Mr. **Weiss**. A few days after FDA approved the emergency use of albendazole, however, your agency's Office of General Counsel advised that the law does not give FDA the leeway to allow for the emergency use. I am referring to an October 12, 1979, memorandum from Mr. Fred Degnan, who was then, I think, head of the Office of General Counsel.

[The memorandum referred to follows:]

Dr. Guest

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFAR
OFFICE OF THE SECRETARY
Office of the General Counsel

DATE: October 12, 1979

TO : Dr. Myron Rosenberg

FROM : Fred H. Degnan FHD

SUBJECT: Investigational New Animal Drug Applications

Two issues have surfaced recently which have called into question the permissible extent of an investigational new animal drug exemption under Part 511 of 21 CFR. One instance involves the expanded INADA approved for albendazole. The other instance involves the use by universities of prostaglandins not for the purpose of investigating the effectiveness of prostaglandins but rather for the purpose of uniformly bringing animals into estrus as a prerequesite to diverse, non-prostaglandin related testing.

Sections 409, 505, and 512 of the Act contain provisions allowing for the exemption from the strict premarket clearance approval requirements found in those sections as long as the exempted product meets the investigational drug status requirements spelled out in companion regulations. The regulations found in Part 511 do not expressly address the permissible scope of an INAD filed under 512(i). In an effort to determine more fully the intent and meaning of the investigational drug provisions found in the various sections of the Act, I have performed a review of the legislative history of the Act.

The legislative history of the Food Additive Amendments of 1958 contains the following statement from Commissioner Larrick regarding the then proposed section 409(h) (now 409(i)) of the Act:

> Chemicals could be exempted from meeting detailed requirements of the Bill if they were intended for research studies to determine their safety or if it were found that for other reasons such an exemption was entirely consistent with the protection of the public health. Hearings before the Subcommittee on the Committee on Interstate and Foreign Commerce, House of Representatives, 58th Cong. p. 447.

As a result of the 1962 Drug Amendments section 505(i) of the Act was expanded to require the establishment and maintenance of adequate records in making appropriate reports on the investigational use of drugs. The legislative history of the Drug Amendments of 1962 expressly clarifies that section 505(i) was expanded to "facilitate the evaluation of safety and effectiveness of the new drug when an application was filed." Committee on Interstate and Foreign Commerce, H.R. Report No. 2462, 87th Cong., 2nd Sess., p. 10. The legislative history of the 1962 amendments also makes clear that 505(i) was expanded in light of the thalidomide tragedy and would give FDA a greater control over preclinical tests. See September 27, 1962, Congressional Record, p. 19895. Senator Estes Kefauver definitely characterized the scope of Section 505(i) as reflecting a compromise allowing analytical reports made by investigators to drug manufacturers to be considered as part of the data "the Secretary can require drug manufacturers to furnish him prior to the submission of the new drug application in order to enable him to evaluate the safety and effectiveness of a drug in the event the new drug application for it is filed." October 3, 1962 Congressional Record, p. 20869. The Senate's summary of the Drug Amendments of 1962 adopted Senator Kefauver's interpretation of section 505(i):

> Further regulations have specifically authorized to require as a condition of exemption of experimental drugs the keeping of records and making of reports on the investigation that will enable the Secretary to evaluate the safety and effectiveness of a drug if later an application is made for approval of the drug for commercial distribution. This authorization is not limited to drugs intended for human use. This should make it possible for FDA scientists to familiarize themselves currently with the emerging scientific data on drugs before a new drug application or antibiotic application for approval for commercial distribution is made. Page 5 of the summary.

The drafters of the 1968 Animal Drug Amendments did not apparently spend a great deal of time on the issue of investigational drugs. From the little that was said, however, it appears that a primary purpose of providing for an investigational new animal drug application was to ensure the collection of data which would facilitate the approval of a new animal drug application. This is supported in the statement by the Honorable James L. Goddard, then Commissioner of Food and Drugs:

> New regulations setting forth the rules for veterinary investigational drugs have been issued by separating the requirement for veterinary drugs from those established for human drugs, we have often given attention to the particular need for the development of laboratory and clinical data in

> this area with special reference to the protection of meat, milk, and eggs derived from animals used in investigations. Animal Drug Amendments of 1965, Hearing Before the Subcommittee On Public Health and Welfare of the Committee on Interstate and Foreign Commerce, House of Representatives, 89th Cong., 2d Sess., p. 28. (Emphasis added.)

The legislative history of the New Animal Drug provisions also makes clear that those provisions are not to be treated differently from the new drug provision from which they are directly derived. Congress wished to separate human and animal drugs for the purpose of clarifying the way that overlapping regulatory controls would be administered in the future but no change was intended in the basic scientific and legal requirements for approval. See House of Representatives Report No. 875, 90th Cong., 1st Sess., (1967).

The legislative history of our Act helps, therefore, to interpret section 512(i). 512(i) contains the following language:

> To the extent consistent with the public health, the Secretary shall promulgate regulations for exempting from the operation of this section new animal drugs ... intended solely for investigational use by experts qualified by scientific training .... Such regulations may at the discretion of the Secretary ... provide for conditioning such exemptions upon the establishment and maintenance of ... data ... obtained as a result of such investigational use of such article as the Secretary finds will enable him to evaluate the safety and effectiveness of such article in the event of the filing of an application pursuant to this section ....

The section and the history may be read together as delineating that the primary purpose of the investigational drug provisions as interpreted by the Congress was to provide a means for legally being able to investigate the safety and effectiveness of a drug for the purpose of collecting data to satisfy the premarketing clearance requirements spelled out in the Act. Certainly, the underlined language from section 512(i) above reflects that construction.

In light of the foregoing, it would seem prudent that the Bureau closely look at its policies regarding investigational new animal drug applications. As seen, the primary thrust of the statute and its history is that an exemption is to allow testing necessary for the development and approval of a new animal drug. Should the Bureau be of the opinion that other uses of the investigational new animal drug regulations are appropriate, I believe that the Bureau should develop a policy or guideline identifying the specific permissible areas of research. I emphasize that I do not think that the legislative history and plain language of the Act give the Bureau much leeway, particularly as the Act has been refined since 1958. Some limited exceptions may be in order. It is important for the Bureau to flesh out those exceptions so that the Bureau's approach to handling INADs will be consistent.

Mr. Drozen. Mr. Chairman, let me correct you. Mr. Degnan is also a staff attorney.

Mr. Weiss. A staff attorney, OK. The memorandum was from him.

Dr. Crawford. I think, Mr. Chairman, that there was disagreement, as you have correctly pointed out, as to whether or not this could be done. And as we mentioned yesterday, there always will be within the legal staff and the scientific staff legitimate differences of agreement.

Mr. Degnan's memorandum may have represented that, and may not have represented the Office of General Counsel.

Mr. Weiss. Does the Food, Drug, and Cosmetic Act, to your knowledge, authorize use of an unapproved new drug for purposes other than to facilitate development and approval of a new animal drug through investigations of its safety and efficacy?

Dr. Crawford. There was a question about that. We were given to understand, as you also know from material that you have, that the Deputy Commissioner of FDA eventually ruled after hearing all points of disagreement and agreement that it was possible to do this legally, and therefore it was done. The decision was made at that level.

Mr. Weiss. Do you have a document from the Office of General Counsel establishing such a ruling?

Dr. Crawford. We will have to check and see, Mr. Chairman.

Mr. Weiss. Would you, because we have not seen that. It would be worth having it for the record.

Dr. Crawford. OK.

[FDA has advised the subcommittee that: "There is no document from the Office of the General Counsel regarding the decision on albendazole made by Deputy Commissioner Gardner."]

Mr. Weiss. In his October 12, 1979, memorandum, Mr. Degnan states: "[T]he primary thrust of the statute and its history is that an [investigational new animal drug] exemption is to allow testing necessary for the development and approval of a new animal drug" and "the legislative history and plain language of the act [do not] give the Bureau much leeway."

That was the position as of October 12, 1979. Having received that advice, you maintain that CVM still believes that the albendazole program met the requirements of the act, because you received another ruling from the Office of General Counsel? Is that your testimony?

Dr. Crawford. Yes.

Mr. Weiss. Well, we would appreciate your documenting for the record that position by the Office of General Counsel.

Dr. Crawford. Yes.

Mr. Weiss. Under FDA's regulations, a sponsor may not charge for a new animal drug until it has been approved. Did FDA authorize the sponsor to charge for albendazole?

Dr. Crawford. Yes. The sponsor could recover cost of the drug in those few States where it was allowed to be sold. As you know, it was sold under tightly controlled conditions in order to ameliorate the outbreak of liver fluke disease that was ravaging a number of States at the time.

Mr. **Weiss**. But the regulations are clear, are they not, that a sponsor may not charge for a new animal drug until it has been approved. And albendazole was not an approved drug, was it?

Dr. **Crawford**. As I mentioned earlier, the decision of the Food and Drug Administration at that time, which was done by the Deputy Commissioner of FDA, was that this product could be sold, and that it also could be distributed in States under tightly controlled conditions. It was responding, as you also know, to the fact that there was no drug to treat this condition on the market.

Mr. **Weiss**. Are you telling us that you have a ruling from the Office of General Counsel?

Dr. **Crawford**. I am telling you from the Office of the Deputy Commissioner.

Mr. **Weiss**. Although FDA's regulations prohibit charging for a new animal drug until it has been approved, the Office of Deputy Commissioner ruled that charging for an unapproved drug was permissible in this instance?

Dr. **Crawford**. It was a special circumstance.

Mr. **Weiss**. Well again, would you submit for the record whatever documentation you have of that position?

[The information requested follows:]

There are no documents we can locate in which this issue was recorded. However, it has been longstanding policy that sponsors may charge for investigational drugs to recover costs and this would not be considered commercialization.

Mr. **Weiss**. Dr. Crawford, on October 15, 1979, you wrote: "Obviously, some portions of the INAD regulation requirements would have to be waived" for albendazole.

[Dr. Crawford's October 15, 1979, memorandum follows:]

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Acting Commissioner, FDA

DATE: OCT 15, 1979

FROM : Director
Bureau of Veterinary Medicine, HFV-1

SUBJECT: Albendazole - Smith/Kline - Liver flukes.

Mr. Ebright of the Smith/Kline Company will telephone you either on October 12, 1979, or October 15, 1979, to discuss our offer to Smith/Kline that Albendazole be made available under an expanded INAD.

To reiterate:

1. We offered to establish procedures for investigational use of the drug in the fluke areas.

   Note: Obviously, some portions of the requirements in the regulations for INAD will have to be waived.

2. As a condition, we asked that an additional depletion study be started immediately and that data be submitted no later than six months from now.

   Note: Smith/Kline representatives told us informally on October 11, 1979, that this is not possible because it will be early January before radiolabeled drug will be available.

The Bureau of Veterinary Medicine has begun the task of laying out the details involved in controlling and monitoring the use of the product.

1. A task group consisting of BVM, EDRO, ACRA, and OCC has been formed to establish a detailed procedure.
2. Preliminary discussions have been held with USDA to see what support we can get from their field people--more negotiations needed.
3. Educational material is being prepared--plans to involve the cattlemen associations and the Ag. Extension service are underway.

Although we still have many details to work out, I believe a workable system is possible. I suggest at this point:

(1) That BVM move ahead as quickly as possible to lay out an overall system of control,

(2) that we then set up a meeting with Smith/Kline representatives to go over the system as we propose,

(3) that we then get a final decision from Smith/Kline on their providing albendazole under the proposed procedure.

Note: We can anticipate some negotiating will be necessary.

Mr. **Weiss**. What was the legal basis for relieving the sponsor of its obligation under the agency's INAD requirements?

Dr. **Crawford**. Well again, it was a special circumstance, and we can provide what documentation we have for the record.

I was pointing out to the Acting Commissioner that this was an unusual situation involving an emergency use of the product, because of the nationwide problem that we were having with liver fluke infection, and which we believed compromised both human and animal health. And also bringing to his attention that the only alternative to doing this was to allow the use of hexachlorethane which had been found to be a carcinogen by the National Cancer Institute, and also was not an approved drug.

Therefore, it was outside the purview of FDA, and outside the control. So something had to be done. And what was done was the emergency authorization of albendazole.

Mr. **Weiss**. On October 1, 1979, FDA told the sponsor that the "emergency program" was "intended to allow limited investigational studies and not for widespread use of the drug."

[FDA's October 1, 1979, letter to the sponsor is in the record.]

Dr. **Crawford**. That is true, and we did not authorize nationwide use, as you know. We limited it to certain States, and only on evidence that liver fluke infection was a problem, and that there was no other way of dealing with the problem.

Mr. **Weiss**. Five years later when the drug was removed from the market, in how many States was albendazole authorized?

Dr. **Crawford**. Seventeen.

Mr. **Weiss**. Do we know how many food-producing animals were given albendazole in 1984?

Dr. **Crawford**. We can submit that for the record, Mr. Chairman. I am not aware of exactly how many were given in that year.

[The information requested follows:]

The treatment records of 1984 are incomplete. No meaningful estimates can be made.

Mr. **Weiss**. Would you agree that it was probably more than a million?

Dr. **Crawford**. I just could not say. I would think that it would be in the hundreds of thousands, and perhaps either approach 1 million or be 1 million.

Mr. **Weiss**. Thank you.

During an October 26, 1979, meeting, FDA instructed the sponsor that "continuation of the expanded INAD program was contingent on stringent control of the use of the drug."

[The memorandum of that meeting follows:]

Ⓑ

October 26, 1979

Hold File
for future
Disclosure

MEMORANDUM OF CONFERENCE

Attendees: Dr. George Scott
Smith Kline

Ms. Helen Birkhead
Smith Kline

and

Dr. Lester Crawford, HFV-1
Dr. Terence Harvey, HFV-2
Dr. Robert Scheuplein, HFF-6
Dr. Gerald B. Guest, HFV-9

Subject: Albendazole - INAD

This meeting was requested by Dr. George Scott as a followup to the telephone conversation of Mr. Ebright, President of Smith Kline and Mr. Sherwin Gardner, Deputy Commissioner, FDA.

The conversation between Mr. Ebright and Mr. Gardner concerned Smith Kline's indication that the company is interested in providing Albendazole in the liver fluke areas for the liver fluke crisis under an expanded INAD procedure. This meeting was for the purpose of discussing details on the requirements of the Food and Drug Administration insofar as the INAD procedure for this drug and for this use is concerned.

The Smith Kline representatives were handed a copy of an outline of the FDA's position on how the product should be moved in interstate commerce and what controls were necessary to see that the product caused no risk to man by becoming a part of man's food. A copy of FDA requirements under this particular circumstance is attached. These requirements were suggested by a working group of individuals including representatives from ACRA, EDRO, Office of General Counsel, and the Bureau of Veterinary Medicine.

Smith Kline representatives agreed after discussing the details of FDA's presentation to go back to Smith Kline's management for a final decision on Smith Kline's position on the matter. It was agreed that Ms. Birkhead would call Dr. Crawford no later than November 2, 1979 to give him Smith Kline's decision or to at least give him a status report at that time.

It was agreed at the conference that we have enough information to declare a legitimate emergency need in Florida, Texas and Oregon for use of the drug in cattle and sheep. Dr. Crawford suggested that other States having a liver fluke problem should furnish documentation to the Agency in the form of a petition requesting inclusion into the program. Dr. Guest agreed to work through the Federal State Relations staff of the FDA in order to make other States aware of the program and to disseminate information on what documentation was needed to establish an emergency need in their particular state.

Preparation will also be made for conferences to discuss content of labeling and content of the two forms necessary as described in the product flow chart attached. Ms. Birkhead will meet with the Ruminant Division of Scientific Evaluation in order to work out the details on these items. Dr. Guest will brief Ruminant Division personnel as to the events to this time.

Dr. Scott and Ms. Birkhead furnished Food and Drug with a copy of labeling for Albendazole used in England as well as a copy of a paper stating locations of Norden distribution centers in the United States.

It was made clear to the Smith Kline representatives that continuation of the expanded INAD program was contingent on stringent control of the use of the drug as well as Smith Kline's conscientious pursuit of remaining items necessary for a NADA approval.

Gerald B. Guest, DVM

Attachment

CC: Attendees
Dr. George Scott, Smith Kline Company
Dr. Crandall, HFV-200
Dr. Baldwin, HFV-100

GBGUEST:FR:10/31/79

ALBENDAZOLE- INAD

Product Flow		**Control**
Norden Laboratories Lincoln, Nebraska	-	Raw product from Mexico, K.C. District to monitor.
	-	GMP's K. C. District.
	-	Records on shipment to distribution Centers, K.C. District.
Norden Distribution Centers (Locations to be determined)	-	Drug Storage and Inventory, FDA field Personnel to monitor.
	-	Veterinarian orders drug, gives name(s) of producers and numbers of doses required. (Initial Contact Form*). FDA monitors records.
	-	Drug shipped to veterinarian, FDA monitors records.
	-	21CFR511.1(a)(b). Records submitted to INAD, quarterly.
Practicing veterinarian	-	Veterinarian dispenses drug, discuss w/d-time and special precautions with producer (Educational Material Furnished By FDA).
	-	Veterinarians visited (randomly) by USDA Field Personnel and Regional Veterinary Medical Officers.
	-	Veterinarian Furnished form (Followup*) to record information on drug use, adverse reactions, reproduction, etc. (To

Mr. **Weiss**. Dr. Crawford, are you satisfied that albendazole was distributed in the stringent manner required by the program?

Dr. **Crawford**. Yes. Subsequent to the cessation of the emergency authorization, which as you know occurred this year, we had a review of the distribution of the product, which was the subject of a high level meeting at FDA headquarters in which field officials from FDA met with headquarters officials and reviewed relevant information in this regard.

Their conclusion was that although FDA had to always be vigilant in the distribution, and there had been some problems at least in one State that caused me to write a letter cautioning State officials about distribution problems, that there was nothing that followed a pattern that would justify prosecution.

And so I would have to say in answer to your question, Mr. Chairman, that there were distribution problems, but not of the magnitude to warrant FDA taking legal action.

Mr. **Weiss**. But again, just so that I can be sure I understand your answer. The question that I asked was whether you are satisfied that the drug was used in the stringent manner required by FDA when it authorized emergency use of the drug?

Dr. **Crawford**. For the most part, it was. It was confined to the States that we authorized. And as I said, our review of the situation said that it was by and large followed.

Mr. **Weiss**. Let me note for the record that, on the basis of several inspections, FDA officials in the latter half of 1984, saw in the widespread misuse of albendazole, a "complete abrogation of the agreement with the sponsor * * * and significant illegal activities, i.e., a situation completely out of control."

Now how does that square with your view of it?

Dr. **Crawford**. That was the opinion of some individual, I assume from what you are saying. But let me point out again that there was a review of this this year, and that was not the conclusion of the review committee. That represented an individual opinion as far as I know not based on evidence.

Mr. **Weiss**. Dr. Settepani, do you have any familiarity with the agency's review of whether distribution and use of the drug was stringently controlled?

Dr. **Settepani**. No, sir, I do not.

Mr. **Weiss**. Dr. Crawford, the statement that I read to you was made, not on the basis of an individual's view, but rather on the basis of several inspections.

Dr. **Crawford**. May I see the memorandum, Mr. Chairman? I am not familiar with that.

Mr. **Weiss**. Yes. It is a memorandum dated October 4, 1984, from CVM's bioresearch monitoring staff.

[The memorandum referred to follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date October 4, 1984

From Bioresearch Monitoring Staff (HFV-234)

Subject Summary of Field Findings: Albendazole Emergency Agreement, INAD 2433 and 2434; HFV-234 Assignments 7/20/84 and 7/23/84, et al., and INAD 1641, Albendazole

To Files

The following is a summary of the findings from the Establishment Inspection Reports (EIRs) received to date regarding Albendazole. These inspections were initiated in response to HFV-234 assignments of 7/20 and 23/84 et al to monitor the Albendazole situation. We expect additional EIR's to be received based on assignments issued and telephone reports of in-process investigations. We also expect a significant number of regulatory recommendations from district compliance offices based on the conclusions and recommendations of these EIR's.

These EIR's demonstrate a complete abrogation of the agreement with the sponsor, Smith-Kline Animal Health Products and significant illegal activities, i.e., a situation completely out of control.

In addition, we have recommended (9/4/84) termination of the exemptions for INAD 1641 and 2033, Albendazole based on findings resulting from four (4) other EIR's (Georgi, D'Ver, Carroll, Cuningham) for use in commercial breeding colony dogs and cats, since these were purely commercial uses of albendazole under the guise of controlled clinical investigations conducted under investigational exemptions.

In addition, NWK-DO conducted an EIR of Biodynamics, Inc., the laboratory which performed the long-term carcinogenicity study in rats with albendazole. We issued an NAF letter to that laboratory and SKAHP on 9/26/84.

Also, review of the albendazole INAD jackets revealed numerous unapproved species being treated with albendazole under the emergency agreement (goats, lactating sheep, cattle, zoo animals and commercial buffalo and buffalo/cross herds). In addition to incomplete records, it was used for unapproved parasites (tapeworms, stomach worms, lungworms) and as a general wormer.

Several major factors in SKAHP/Norden's loss of control of the situation have surfaced including:

1. The approval of commercial labeling claiming safety and effectiveness against other parasites besides liver flukes; and the use of promotional brochures widely distributed throughout the country.

2. The lack of an adequate control procedure by Norden's distribution centers to prevent drop shipments to unapproved states and counties.

3. The failure to have adequate SOP's in place at all distribution centers and to provide proper training for sales personnel in both approved and unapproved states.

4. The failure by SKAHP to properly monitor the Norden distribution system, including sales to wholesale distributors not serviced by veterinarians; and the encouragement of sales by allowing use of presigned pads of order forms which are then completed by the Norden distribution centers or wholesalers based on client telephone orders or contacts with salesmen (employed by Norden and private wholesalers)"

The failure to provide for accountability between order forms and treatment forms, since we have reports of a high percentage of treatment forms not being prepared and/or submitted to SKAHP.

6. SKAHP/Norden have recently begun a three month "price reduction program" and a 'delayed billing program" for volume orders, pure commercialization and what we consider a continuation of the practice of selling albendazole (to which the agency agreed in priniciple, i.e. cost recovery).

Summary of EIR's

A. EIR - John M. Morton, D.V.M., Athena, Texas - 1/7-10/83

(1) Commercial sale to an undercover FDA investigator
(2) Failure to complete treatment forms
(3) No legitimate doctor/client/patient relationship

B. EIR - Norden Labs, Inc., Lincoln, Nebraska - 2/7-9/84

(1) No SOP or written agreement listing terms of the distribution procedure
(2) Monitoring consists of only assuring that shipments are to veterinarians - no checking for approved states and approved counties.

C. EIR - Norden Labs, Inc., Lincoln, Nebraska - 7/3/84

Distribution information 1/1/84-6/29/84

D. EIR - Thomas A Carroll, D.V.M. - 7/2 and 8/7/84 and DOC Sample 84-469-269

(1) Albendazole used as a routine treatment for a commercial beagle breeding colony under the guise of a clinical investigation under INAD #2033. No safety study being conducted

(2) Product sold to Dr. Carroll at $325.00 per gallon

E. EIR - John M. Cunningham, D.V.M., Elgin, Iowa - 3/20/84

(1) No controlled clinical study being conducted - INAD 1641

(2) SKAHP informed Dr. Cunningham that he couldn't receive albendzole under the emergency agreement since he was located in an unapproved state, Iowa, but could receive it as part of a study. He continued to receive shipments of the drug without conducting

any study or supplying any reports.

F. See list of attachments

G. EIR - Bio-Dynamics, Inc. East, Millstone, NJ - 6/12-15, 18-21/84 (1)-(5)

H., I., & J. See list of attachments

K. Memorandum and personal report of sales promotion of Albendazol prepared by Dr. W. B. Bixler, 8/2/84

L-Q. See list of attachments

R. ORL-DO Memorandum re AID Lboratories and Stockman's Supply, wholesalers of albendazole in Florida, dated May 8, 1984. (See (UU), (YY), (ZZ) and (AAA) attachments of EIRs of Florida Veterinarians)

S. ORL-DO Memorandum re extra label use of albendazole by Dr. Ross A. Hendry, D.V.M., dated July 13, 1984.

T. Copies of correspondence and treatment forms from INAD #2433

(1) Note that these treatment forms show dairy goats, dairy cows, and lactating sheep treated for lungworms tapeworms, and roundworms.

(2) Questionable veterinarian/client/patient relationship; farmers treat their own sheep

W. EIR - Staples Veterinary Clinic, Staples, Minnesota - 8/9/84

(1) No pre- post- or combination treatment forms have ever been sent to Norden or SKAHP. They were never told to send the forms anywhere. They have been using drug sing August 1982

(2) Questionable veterinarian/client/patient relationship; farmers treat their own sheep

X. EIR - Norden Labs, Inc., Brooklyn Park, Minnesota, Distribution Center - 7/31/84

(1) Using an Albendazole Distribution SOP dated December 1982 (vs. the April 84 and August 84 versions)

(2) The only monitoring is to see if a veterinarian's name is on the order form ("Dr." or "DVM").

(3) They have been shipping albendazole to Northern Wholesale Veterinary Supply which is being investigated by MIN-DO for illegal distribution of veterinary drugs (a Dr. Hauser, D.V.M.) with a view towards injunction.

Y. See list of attachments

Z. EIR - Norden Labs, Inc., Englewood, CO Distribution Center 7/31-

8/1/84

(1) The only monitoring is to see if a veterinarians name is on the order form ("Dr." or "DVM")

(2) Firm has no instructions to determine that customers are in fact veterinarians. Management assumes that sales personnel make that determination. Note that all sales personnel work for Norden out of Lincoln, NE, not the branch distribution centers.

(DOC Sample # 84-204-536/7)

A.A. EIR's and Files on Dr. Abbott D'Ver, White Eagle Labs, Doylesown, PA and Dr. Jay Georgi, Cornell Univ., Ithaca, NY (dog breeding colonies) (See (D), (E), and (HH))

B.B. ORL-DO memorandum re Lion Country Safari, West Palm Beach, FL. use of albendazole obtained under INAD 2433, in zoo animal species.

C.C. EIR - Dr. Ray W. Randall, Bridger, MT - 8/14/84

(1) No post treatment forms for most producers

(2) Norden promotional brochure in veterinarian's client waiting room

D.D. Brochure from Pipestone Vet Supply, Pipestone, Minnesota, offering mail order albendazole. MIN-DO is attempting an undercover buy.

E.E.- G.G. (See list of attachments)

F.F. Preliminary telephone reports of albendazole activities. Numerous documentary samples and regulatory recommendations are in process (9/14/84)

H.H.- I.I. Recommendation for termination of INAD exemption #1641 and 2033, albendazole suspension dated 9/4/84 (see (D), (E), and (AA))

J.J. EIR - David Tanner Vet. Clinic, Russellville, AR - 8/15-16/84
No significant deviations

K.K.- L.L. See list of attachments

O.O. Preliminary telephone reports: 9/19/84 Additional reports of regulatory recommendations in process

P.P. EIR - Dr. Frank J. Skalko, Moose Lake, MN 8/9/84

(1) No pre-, post-, or combination treatment forms have ever been sent to sponsor. Never given any instructions or address as to where to send forms.

(2) No owner signature on one form

(3) Some of the albendazole received by Dr. Skalko was sold to another veterinarian.

(4) One herd of animals was treated where all of the animals were within 45 days of conception at the time of treatment.

Q.Q. EIR - Dr. Nelson H. Duncan d/b/a Uinta Veterinary Services, Roosevelt, UT 8/14-15/84

(1) Incomplete treatment forms in 10 of 24 herds treated; many do not bear owners signature.

(2) Albendazole prescribed and shipped on animal owner's diagnosis without any veterinary observation or tests.

(3) Use of telephone orders to Norden distribution center without completing order forms.

(4) Albendazole prescribed for roundworms and stomach worms

(5) Dr. Duncan was informed by Norden salesman that albendazole was a broad spectrum general anthelmintic.

(6) Dr. Duncan unaware of pregnancy restriction. He has treated animals within the 45 day period of conception.

R.R. EIR - Basin Vet Clinic, Roosevelt, UT - 8/28/84 (Dr. Dennis)

(1) Incomplete pre- and post-treatment forms. All lack one or more of the following: dates, signatures, addresses, species and amount of drugs dispensed

(2) No post-treatment evaluations performed.

(3) Dr. presigns order forms. The Norden salesmen retains the forms and clinic calls in orders.

(4) No pretreatment forms have ever been sent to sponsor or anyone else.

(5) No veterinarian/client/patient relationships - Doctor assumes that parasites, including liver flukes are endemic

(6) In 1980 according to Dr. Dennis, Norden provided a sign which the salesmen placed in his office window, which stated "Albendazole available here"

S.S. EIR - Dr. William H. Lovett, Jr. (Hardee Animal Clinic), Wauchula, FL 8/13-15/84

(1) 50% of treatment forms unsigned by animal owners

(2) Forms lacked required information.

(3) 13 forms never submitted to Norden.

(4) Questionable veterinarian/client/patient relationship - Drugs (albendazole) dispensed without ever seeing animals.

(5) ORL-DO is attempting an undercover buy in Dr. Lovett's office based on availability of 118 pieces of an albendazole brochure available in the doctors waiting room.

T.T. EIR - Town & County Animal Clinic, Gunnison, CO (Drs. Shick & Noone)

(1) No apparent order forms completed. Norden accepted telephone orders.

(2) No apparent pre-treatment forms completed.

U.U. EIR - Dr. James L. Shewmaker, La Belle, FL - 8/15-16/84

(1) No veterinarian/cleint/patient relationship. Norden in Miami, FL mails pads of order forms to Dr. Shewmaker who signs them, and mails them to Norden who ships albendazole to Stockman Supply, Sebring, FL. Based on customer phone orders to Stockman or to the stockman salesman, the albendazole is shipped or delivered to the customer. Stockman completes the treatment forms and sends them to Dr. Shewmaker for signature. Affidavits show Dr. Shewmaker is paid $300/month for only signing the order forms. Dr. Shewmaker has not sent any treatment forms to Norden or SKAHP.

(2) Albendazole was recommended as a general anthelmintic by Dr. Shewmaker to Cleghorn Dairy.

(3) The delivery truck driver for Stockman carries albendazole in his vehicle and stated he would sell albendazole to anyone.

ORL-DO is preparing a seizure recommendation.

V.V.-XX See list of attachments

Y.Y. EIR - Dr. Michael L. Warren, Fort Meade, FL - 8/30-31 & 9/7/84

(1) No veterinarian/client/patient relationship. Dr. Warren is on contract with Life Services, Inc., formerly known as AID Laboratories, Inc. (Note: Previous Regulatory Letters to AID Labs and a Dr. Barnes for distribution of albendazole)

(2) Blank, signed order forms are provided to Norden at a rate of 15-20 per month by Dr. Warren.

(3) Apparently forged client signatures on treatment forms (Product never received according to customer.)

(4) Two instances of albendazole being resold to another wholesaler.

(5) Albendazole promotional brochures displayed in sales room of Life Services (Aid).

(6) Life Services can not account for nearly 9% of the albendazole received between 8/1/83 and 8/1/84 with treatment forms.

(7) Treatment forms incomplete and inaccurate.

(8) Life Services is particpating in Norden's current price discount offer and deferred billing plan.

(9) Life Services provides albendazole to a Mr. E. Lumpkin, a cattle broker, for shipment with feeder calves to Oklahoma (unapproved state) with the knowledge of Life Services.

OL-DO has collected Documentary Samples 84-333-663/64 and is recommending regulatory action including seizure.

Z.Z. EIR - Dr. Charles Field, Arcadia, FL, 8/15-16/84

(1) Presigned blank order forms sent to Norden, Miami, FL.

(2) Several treatment forms incomplete.

A.A.A EIR - Dr. Frank H. Platt, Okeechobee, FL - 8/23-24 & 27/84 (M&M Supply Co.)

Note: Prior NAF letter to Dr. Platt 6/83

(1) Presigned blank order forms sent to Norden, Miami, FL.

(2) Sales of albendazole to M&M Supply Co. by Dr. Platt on consignment. Dr. Platt is paid cost + 2 1/2% by M&M Supply

(3) No treatment forms completed since May 1984 and no other records of names of clients receiving albendazole since May 1984. (Treatment forms were completed by M & M Supply van drivers when they were available prior to May 1984).

(4) Three dairy farms were visited. One dairy farmer tated that they do not have a fluke problem, and one (Brighton Dairy) stated that they had not seen Dr. Platt in three years although they continue to receive albendazole as a general anthelmintic.

(5) Most of the albendazole sold by M & M Supply is sold by their delivery van drivers.

(6) Norden salesmen have informed Dr. Platt of the three month price reduction program and the delayed billing program.

(7) Dr. Platt admits promoting the sale of albendazole orally and with the promotional brochure supplied by Norden.

(8) Larsen Dairy, Okeechlobee, Florida is receiving albendazole for a milking he~~a~~rd with 6,169 currently lactating animals. Animals are treated near the beginning of the freshening period (about 60 days).

(9) Brighton Dairy, Okeechobee, Florida, has received albendazole as

a general anthelmintic from Dr. Platt. They do not have a fluke problem and have not seen Dr. Platt in three years.

B.B.B Additional telephone reports on in process field investigations: Memo to the files

C.C.C. Memo telecon 10/2/84; Hank Hear, Stockton, California Resident Post/DE Baker, HFV-234

(1) Dr. Woodward, operats Veterinary Services, Inc., Modesto, California, a veterinary supply firm which supplies albendazole to feedlots, auctionyards, other wholesalers, a meat packing firm and dairy operations. No veterinary/client/patient relationship exists.

(2) Dr. Woodward is involved with several other businesses previously involved in illegal distribution of veterinary drugs.

This investigation is ongoing at the present time.

We will update this summary as new EIR's are received.

Darrell E. Baker

Darrell E. Baker

DEBaker:km:10/2/84
Revised:10/4/84

DRAFT

ALBENDAZOLE

EIR's	Number of EIR's Demonstrating Violation
Extra-Label use: (other species, other parasites, dosage, etc. Treatment during pregnancy, lactating animals, etc.)	13
No veterinarian/client/patient relationship	11
Promotional brochures, et al promotional activities available to clients	6
Incompleted or no order forms treatment forms prepared	15
Inadequate or out of date SOP's for Distribution (Norden)	3
Illegal sales to : (commercialization)	
other wholesalers	6
other veterinarians	4
direct to customers/users	11
Mail order Albendazole	1
Telephone orders accepted	2
Price discount offer and delayed billig program	2

Note that this tabulation includes only EIR's received to date and does not include telephone reports of in-process investigations. Also note that each EIR may show multiple violations.

EIR's received to date: 21 (10/4/84)

Percentage of EIR's demonstrating violations

Extra-label use	62%
No veterinarian/client/patient relationship	52%
Promotional brochures available to clients	29%
Incomplete or no order/treament forms	71%
Inadequate SOP's for distribution	100%
Illegal Sales to:	
other wholesalers	29%
other veterinarians	19%
direct to clients	52%
Mail order albendazole	0.05%
Telephone orders accepted (Norden and wholesalers)	0.095%
Price discount offer and delayed billing program	0.095%

Mr. WEISS. Dr. Tufts, would you approach the table? I believe that you wrote this memorandum. Perhaps you and Dr. Crawford can look at it and respond.

[Pause.]

Dr. CRAWFORD. Mr. Chairman, we are ready to respond. If I may respond first, and then ask Dr. Tufts to also respond.

Mr. WEISS. Please.

Dr. CRAWFORD. This represented basically the quality control that FDA felt obligated to perform on distribution of albendazole in order to assure that it was kept, primarily we wanted it kept, within those States that had been authorized for use, wherein we had control mechanisms in place through the State Veterinarian's Office, the USDA's Animal and Plant Health Inspection Service, and other individuals.

On the basis of these particular investigations, we believed that a problem was developing, and one that needed to be brought to the attention of FDA. These were also among those investigations that were analyzed in the meeting that I just referred to on the overall problem of whether or not there had been an indictable offense with respect to albendazole.

And these problems, we believed, correctable. And also by this time, as you know, we had received a memorandum indicating that further approval of the product on an emergency basis was probably not consistent with recent research results. So we were moving at this point to take it from the marketplace.

And Dr. Tufts may want to respond differently, or to elaborate.

Mr. WEISS. Dr. Tufts.

Dr. TUFTS. I am Dr. Tufts. I am the manager of the Bioresearch Monitoring Program for the Center for Veterinary Medicine.

Mr. WEISS. How long have you been with the Bureau?

Dr. TUFTS. I have been with the Bureau, I guess, 10 or 12 years. And since the early 1980's, I have been in this present position.

Mr. WEISS. Would you comment on what that memorandum says. What is meant by the FDA officials' seeing in the widespread misuse of albendazole "a complete abrogation of the agreement with the sponsor * * * and significant illegal activities, i.e., a situation completely out of control?"

Dr. TUFTS. It seemed to be that the situation has evolved since the original initiation of use. And at this point in time, these violations or problems seemed to have arisen that demanded a summary of this nature. And this was a result of our simple surveillance inspection.

Mr. **Weiss**. So that the view that you were expressing in that memorandum and the view of agency inspectors was that the stringent control requirements of the emergency program were not being met at that point?

Dr. **Tufts**. Yes, sir.

Mr. **Weiss**. Thank you. Mr. Walker.

Mr. **Walker**. Thank you, Mr. Chairman.

Let me try to clarify at least in my own mind some of the things with regard to albendazole here.

Before FDA's approval of the use of albendazole as an emergency investigational new drug, were there any other approved drugs available for the treatment of liver flukes?

Dr. **Crawford**. No.

Mr. **Walker**. As I understand it, hexachloroethane was being made available illegally during the 1970's.

Is that correct, and was that a result of the fact that no legal drug was on the market?

Dr. **Crawford**. Yes. One of the things that we would see, Mr. Walker, that in a regulatory vacuum, that is when no drug is approved for a certain condition, be it human medicine or veterinary medicine, it creates a black market, at least for some individuals, and gives a rationale for using these drugs illegally.

It is up to us to see that a black market does not develop. I do not mean to shirk our responsibility. But hexachloroethane was really the only thing that they could physically obtain to treat liver fluke infection, and we believed that to be a gross public health threat.

Mr. **Walker**. In the absence of an approved product, I would imagine that the agency came under some considerable pressure even from Members of Congress to approve albendazole on an emergency basis.

Is that a fair statement?

Dr. **Crawford**. We came under pressure from various elements including our own conscience. The Congress was interested. Also, livestock producers, and a variety of other groups, the cattlemen's associations, et cetera.

Let me say also that at that point, it is clear that we have the authority at any point delegated to us to just go ahead and approve a drug, I mean to put it on the market. In the case of this product, we had reason to ask for another study which we knew was going to take some time.

So rather than approving it, we adopted an interim position, which was this emergency authorization.

Mr. **Walker**. So it was fairly close to being approved anyway, but you felt that there was one more study needed?

Dr. **Crawford**. Yes.

Mr. **Walker**. But given the fact that it was there at that point, is it fair to speculate that if you had not approved this or any other drug for treatment of liver flukes, that the black market would have developed for albendazole much as it had for hexachloroethane?

Dr. **Crawford**. It certainly would. Because at that time, albendazole was approved in virtually every other country in the world, some 64 countries in the developed world that have drug approval processes.

Mr. **Walker**. And is it still being used in those countries?

Dr. **Crawford**. Yes, it is. This is the only major country that it is not approved in.

Mr. **Walker**. And I understand that you also have some further data with regard to albendazole that has come to you from the manufacturer.

Can you tell us what the status of that is?

Dr. **Crawford**. Yes. This is still an active file, and the manufacturers have recently submitted information which they purport will exonerate this drug from any toxicological problems, and therefore make it approvable.

Let me hasten to point out that we have not evaluated that at this point, and so we have no position on the value of that data in approving this drug. Although it is the sponsor's position that the drug is now exonerated.

Mr. **Walker**. And that is under investigation at the agency at present?

Dr. **Crawford**. Yes.

Mr. **Walker**. Thank you, Mr. Chairman.

Mr. **Weiss**. Dr. Crawford, let me see if I understand your position clearly and accurately.

Are you saying that whenever the Center for Veterinary Medicine concludes that there is a disease in, say, cattle, for which there is no approved drug, that FDA has the authority to approve on an emergency basis any drug which, according to a sponsor, will cure the disease, even though the drug has not met the premarket approval requirements of the Food, Drug, and Cosmetic Act? Is that what you are telling this subcommittee?

Dr. **Crawford**. Mr. Chairman, please indulge me for just a moment. I am trying to be direct and answer with a yes and no when I possibly can.

Mr. **Weiss**. And I am trying to understand.

Dr. **Crawford**. I know you are. I am very sorry that I am going to need to take about 30 seconds here. This is the only time that we have ever done this in the Center for Veterinary Medicine. It is the only time that we have ever had that gray area between approval and the investigation of the drug.

We do not expect therefore that it will ever be done again. But in this particular case circumstances had developed that there was no drug on the market to treat this disease with. We knew that however many head of cattle that needed to be treated, you said a minute ago 1 million per year, and I did not dispute that figure, it may be that many, were either going to die or were going to become diseased prior to going to market whenever they went if they were not treated.

This posed a threat obviously to animal health and also to human health. Diseased animals are not as safe to consume as nondiseased. The other thing is that the drug is intended to be used only in mature animals, those not immediately intended for market.

We believed and have now satisfied ourselves that we were able to implement a 6-month withdrawal time, so that the drug would not be in that animal system at the time of consumption. And then the final point that I would make, again talking a little too long on the subject, is that it was approved in countries all around us. They did not have the regulatory concerns that we did.

And although we fell short of an out and out approval, we believed that we needed to do some more research prior to approving it, and we knew that if we had this emergency authorization, that it would be retractable from the market at any time that we received adverse information. Whereas if we had approved it, we would have to go through the prolonged administrative process.

So we found ourselves in an unenviable position with respect to this drug. But the agency decided that it would not be in the best interests of all concerned to approve it, but to allow its use in those States. Initially, 4 States, later extended to 17, that we believed had to have it. We believed that it posed no immediate threat to human health.

Mr. WEISS. So it is quite clear from that response that this drug was no longer being authorized to be used for investigational purposes, but instead was being permitted for commercial use to cure or prevent a disease.

Dr. CRAWFORD. Within limited circumstances in a small number of States.

Mr. WEISS. Let me ask for another clarification. You are not suggesting that market approval of a drug by other nations is sufficient justification for FDA's authorizing the use of that drug, even though it has not met the premarket approval requirements of the Food, Drug, and Cosmetic Act, are you?

Dr. CRAWFORD. No, I think that we still need to maintain the very high standards, and that we should be No. 1 in public health protection.

Mr. WEISS. So the discussion that you had with Mr. Walker regarding the concern about black market sales of the drug is really irrelevant to enforcement of our laws, is it not?

Dr. CRAWFORD. I am not sure that it is entirely irrelevant, but I am not disagreeing with you. You know, we have to enforce the food and drug laws as they are written. We recognize that they are the most stringent in the world, and it is not unusual for us to find ourselves as the last country to approve a drug, and I am not here to argue for change in that respect.

Mr. WEISS. And, indeed, we have had instances where following the lead of other countries has worked to the detriment of our own society?

Dr. CRAWFORD. That is even true in veterinary medicine, yes.

Mr. WEISS. FDA advised the sponsor of albendazole on December 10, 1979, that if problems occur in the distribution of the drug, or if animal studies then in progress later showed it to be a carcinogen, that "the INAD distribution will be terminated immediately."

[FDA's December 10, 1979, letter to the sponsor follows:]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND [illegible]

DEC 10 1979

Dr. George Scott
Vice-President
Smith Kline Animal Health Products
1600 Paoli Pike
West Chester, Pennsylvania 19380

Dear Dr. Scott:

This letter will confirm the Bureau of Veterinary Medicine's position on the various aspects of the emergency Investigational New Animal Drug (INAD) procedures which we are instituting in order to make the drug, albendazole, available for the liver fluke emergency in the limited areas of the United States. The details here embody the major points of our discussions and correspondence over the past several months. These are:

1. The Food and Drug Administration will allow the limited availability of the drug, albendazole, under INAD procedures in liver fluke infested areas for cattle and sheep. At the present time this includes the affected counties and/or parishes of Texas, Florida, Oregon, and Louisiana. Any petition giving documentation of a need by the state veterinarians in other states will be considered and the distribution can be expanded to other states on this basis. Use will be limited to animals not intended for food (e.g. at least 180 day withdrawal prior to slaughter).

2. Production of the drug will be at the Norden Laboratories facilities at Lincoln, Nebraska. Appropriate GMPs will be maintained by Norden and monitored by the Food and Drug Administration's field forces.

3. Distribution will be exclusively through Norden Laboratories distribution centers and licensed veterinarians in the designated areas. Record keeping procedures and appropriate forms have been developed and agreed to in meetings with Mrs. Helen Birkhead, Smith Kline and FDA representatives.

4. Records will be maintained for two years by Smith Kline and/or Norden Laboratories on veterinarians and producers receiving the drug, and the feedback information received following use of the drug (21 CFR 511.1).

5. Labeling has been discussed and agreed to in correspondence and conferences with Smith Kline representatives (Mrs. Birkhead) and FDA representatives. Among other things, the labeling should specify that this is an investigational animal drug and the indications are for liver fluke treatment only. We understand that the labeling will also include a package insert giving full information on the status of the product (i.e. "FOI" type information).

6. Educational material will be developed and distributed to veterinarians by Norden Laboratories representatives (sales force personnel). Copies of this material should be submitted to the FDA prior to distribution.

7. The FDA will also prepare educational information and will work through USDA, state governments, university organizations, and various associations in order to distribute this information.

8. You have agreed to immediately conduct additional residue depletion studies (radiolabeled) in cattle and sheep. I believe you have recently met with Bureau of Foods personnel in order to discuss the protocols for these studies.

9. You have agreed to conscientiously pursue the remaining work needed in order to receive full NADA approval for albendazole use in cattle and sheep.

10. You understand that if significant problems surface as a result of studies you have in progress or if significant problems occur in the INAD distribution of albendazole, that the INAD distribution will be terminated immediately.

11. Smith Kline (Norden Laboratories) will receive authorization to distribute a quantity of drug sufficient to treat the affected cattle and sheep in the four states named (Texas, Florida, Oregon, and Louisiana). As other states are added, this figure can be modified. I suggest that your representatives meet with Dr. Gerald B. Guest of my staff in order to arrive at an estimate of the numbers of doses needed.

You may consider this letter as authorization for distribution in the four (4) states named above. We will continue to discuss with you specific needs for continued monitoring as we progress through the procedure. Since my aim is to bring relief to the situation as soon as possible, I am hopeful that the product can be available by the spring treatment season (i.e. beginning April 1, 1980).

Sincerely yours,

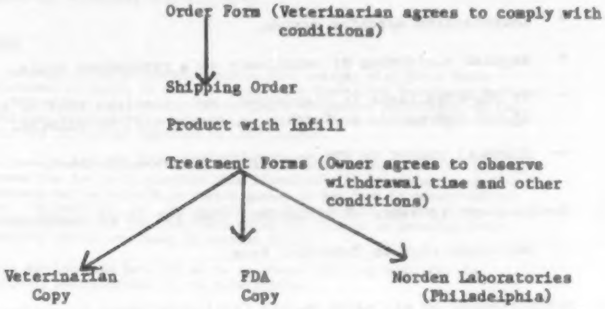
Lester M. Crawford, DVM
Director, Bureau of
Veterinary Medicine

cc: HF-2 (Mr. Gardner)
HFF-1 (Dr. Miller)
HFV-100 (Dr. Baldwin)
HFV-200 (Dr. Crandall)
HFV-120 (Dr. Lehmann)
HFV-123 (Dr. Price)
HFV-5 (Dr. Bixler)
HFV-230 (Mr. Ballitch)
GCF-1 (Mr. Degnan)
HFO-1 (Mr. Healton)
HFF-350 (Dr. Scheuplein)
HFC-13 (Mr. Dykstra)
GBGuest/gcm/12/7/79

Albendazole Emergency INAD Control Procedures

I. Present Procedure

- * Distribution controlled by Norden branches (Copy of SOP attached).
- * Distribution monitored carefully (Copies of customer record and shipment records attached).
- * Documentation (attached).


Order Form (Veterinarian agrees to comply with conditions)
Shipping Order
Product with Infill
Treatment Forms (Owner agrees to observe withdrawal time and other conditions)
Veterinarian Copy
FDA Copy
Norden Laboratories (Philadelphia)

*Forms are reviewed

*If deficiencies occur, veterinarians are reminded of the Emergency INADA conditions and of corrective action required.

- * If non-compliance is reported or suspected of any veterinarian, a Norden representative advises the veterinarian of the conditions of the Emergency INAD. If the veterinarian does not correct the deficiency, no further shipments of Albendazole are allowed.
- * Regular internal audits of branches are conducted by Norden Quality Assurance.

II. Results of Present Procedures

- Branch inspections - no significant discrepancies.
- Compliance site inspection - Applebrook: no notice of adverse findings.
- Compliance site inspection - Lincoln: no notice of adverse findings.

III. Additional Control Procedures Proposed

A. Tighten surveillance of veterinarians' completion of ~~order~~ Treatment forms:

- Computerized matching system.
- Regular monitoring of compliance on a randomized basis.
  - — If non-compliance is discovered, veterinarians will be advised. If not corrected, no further shipments will be allowed.
  - — Biannual report to FDA on results and actions taken.

B. Ensure owner is aware of withdrawal time and other conditions of use.

- — Add owner copy to Treatment Form.

C. Reinforcement of all sales people (including those in non-approved states) on the conditions of the Emergency INAD.

D. Emphasize the withdrawal period and warnings regarding use in veal or dairy animals.

Mr. Weiss. When did CVM's Cancer Assessment Committee conclude that albendazole was an animal carcinogen?

Dr. Crawford. The committee concluded it on July 26, 1984.

Mr. Weiss. On August 23, 1984, Dr. Marvin Norcross, Acting Associate Director for New Animal Drug Evaluation, recommended that you immediately terminate the albendazole INAD program. Dr. Norcross wrote that such a step would be in accord with the conditions of the emergency INAD.

[Dr. Norcross' August 23, 1984, memorandum follows:]

Mr. Dykstra

(LL)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

[illegible] 9/14/84

Date [illegible] 23 [illegible]

From Acting Associate Director for NADE, HFV-100

Subject Emergency Investigational Use of Albendazole - ACTION

To Director
Center for Veterinary Medicine, HFV-1

ISSUE

In response to an emergency situation that existed with liver fluke infections in cattle in certain states, the Center for Veterinary Medicine in 1979 authorized the use, under tightly controlled conditions, of the flukicide Albendazole, an animal drug that is used in many parts of the world but is not yet approved in this country.

The recent evaluation of human food safety studies submitted by the drug's sponsor has led us to conclude that Albendazole is an oncogen, and that consumers may be exposed to unsafe levels of the drug in animal-derived food. In addition, we have received numerous reports of use of the drug that go beyond the permitted uses which are limited to treating liver flukes in cattle and sheep in certain states.

These developments have led us to recommend that you terminate the emergency authorization to use Albendazole.

BACKGROUND

In the summer of 1979, FDA was subjected to considerable pressure from the National Cattlemen's Association and others to make a drug available to treat the serious problem of liver fluke infections that was occurring in certain areas of the country. There was, and is now, no approved drug to treat this disease in cattle and sheep. At the time, SmithKline Animal Health Products (SKAHP), the sponsor of Albendazole, had furnished FDA with data demonstrating the drug's effectiveness as a flukicide but was still in the process of accumulating the information needed to establish a safe level of residues in human food. To solve the drug availability problem, FDA authorized the use of Albendazole to treat cattle and sheep for liver flukes under an expanded, emergency investigational authorization. Several restrictions were placed on use of the drug.

- it was available only through licensed veterinarians; it may not be given to lactating animals;
- a 180-day withdrawal period must be observed before treated animals can be slaughtered for human food; and
- it may be distributed only in specific States.

Letters from the Deputy Commissioner and the Director of the Bureau of Veterinary Medicine sent to the sponsor in the fall of 1979 state that the emergency investigational authorization would be terminated immediately if significant problems surfaced as a result of studies in progress, or if significant problems occurred in the distribution of the drug (TAB 1). At the present time, approximately 900,000 large animals in 19 states are treated with Albendazole each year under the emergency authorization. 900,000

In a memorandum dated August 9, 1984, approximately eight months after submission of the final major study called for by our human food safety guidelines, the Center's Cancer Assessment Committee (CAC) concluded that Albendazole is an oncogen in male and female rats and in female mice (TAB 2).

SKAHP disagrees with the conclusion reached by our CAC. It is important to understand, however, that there is no disagreement between the sponsor and the CAC about the number or diagnoses of tumors observed in the submitted carcinogenicity studies. The disagreement that does exist concerns the relevance of the observed increase in tumors to the safety of drug residues remaining in human food. The sponsor maintains that the study gave a false positive result. Before our CAC and its deliberations on the potential carcinogenicity of Albendazole, the sponsor was informed of our concerns and was invited to present oral and written arguments explaining their position. Documentation of the CAC's deliberations demonstrate that the "corrections" to the data advocated by the sponsor were considered and then rejected by the Committee as being inconsistent with the manner in which carcinogenicity data are evaluated by any regulatory body in this country or, as far as we can determine, in other countries in the world.

Based on results of the carcinogenicity testing we have calculated a level of residues in meat corresponding to a one-in-one-million or negligible lifetime risk of cancer using the procedure described in the Center's human food safety policy for animal drugs. This "safe" level of residue in bovine liver (the tissue of most concern) is 26 ppb which, coincidentally, is the average level of residues found in animals that have been withdrawn from the drug for 180 days. Thus, exposure of consumers to animals withdrawn less than 180 days would be associated with a calculated lifetime risk of cancer that is greater than one-in-one-million.

The validated method of analysis for residues of Albendazole is not sensitive enough to assure that animals have been withdrawn for the required 180-days after being treated with the label-recommended dose of 10mg/kgBW. Continuing to authorize the widespread use in food-producing animals of an oncogen that requires an extended withdrawal period, and without the availability of a regulatory method of analysis to monitor the conditions of safe use of the drug is not, in our opinion, a viable option for the Center.

The calculated "safe" level of residues of Albendazole in milk is 13 ppb. Studies provided by SKAHP demonstrate that drug residues in milk from Albendazole-treated cows deplete from several ppm in the first few milkings to under 10 ppb in about one week. Given these facts, misuse of the drug in lactating dairy cows would be of considerable concern from the standpoint of human health.

A different, but related, concern has arisen in connection with the emergency use of Albendazole. Assignments issued by CVM to our District Offices have resulted in numerous reports of the failure of veterinarians and producers to observe the controls and conditions of use established under the emergency investigational authorization. These violations include:

- failure to identify number and types of animals that were treated;
- incomplete and missing pre and post-treatment forms returned to Norden Laboratories, the formulator and distributor of the drug;
- observed adverse reactions in treated animals that were not reported;
- use of Albendazole in goats, zoo animals and most importantly in lactating dairy cows (our inspectors found that some veterinarians were making the drug available for dairy herds without recommending any discard time for milk);
- shipments of the drug to unapproved states without the necessary paperwork; and
- use of the drug in feedlot animals of a size that makes it highly unlikely that the 180-day withdrawal period would be observed.

From the nature and extent of misuse of Albendazole observed in our field investigations, it is clear that the drug's sponsor has not been diligent in insuring that the conditions of the emergency authorization were being observed. Also, there is evidence that some of the sponsor's employees may have actually promoted misuse of the drug.

On August 13, 1984, CVM staff met with representatives of SKAHP to: (a) describe details of our evaluation of submitted carcinogenicity studies, and (b) discuss possible alternatives to terminating Albendazole's emergency authorization (TAB 3).

It was mutually agreed that requests for a review and/or an appeal of our decision that Albendazole is an oncogen would not be discussed at this meeting although such requests will undoubtedly be forthcoming in the weeks ahead.

At the meeting, the sponsor's scientists informed us that the assay for residues of Albendazole could, in their hands and with minor modification, achieve the sensitivity required to monitor a 180-day withdrawal period. The sponsor offered to help USDA chemists learn the method as quickly as possible. It also agreed to establishing a computer-based audit of the disposition of all drug shipped from its plant under the emergency authorization. Finally, the sponsors indicated it would be willing to discuss the possibility of not permitting livers from Albendazole-treated

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animals to enter the human food chain, and the positive identification of all Albendazole-treated animals, although it was not proposing to adopt either of these measures at the present time.

DISCUSSION AND OPTIONS

Two additional items of information are relevant to the continued emergency exemption for Albendazole.

The first is the fact that the decision by our CAC that Albendazole is an oncogen will certainly delay, and perhaps will preclude, NADA approval of the drug in food-producing animals. Certainly, a more sensitive regulatory method for residues and/or further identification or other demonstration of the safety of long-residing residues in liver will have to be provided by the sponsor. Whether the anticipated NADA withdrawal period of longer than 180 days is likely to be followed in practice, as required by our regulations for NADA approval, is another issue that will have to be addressed.

The second item of information involves the anticipated approval, in the near future, of a NADA for another flukicide. This drug, Clorsulon, has been tested in all of the required toxicity studies, has demonstrated no carcinogenicity, and has been assigned a tentative withdrawal period of 8 days. We anticipate being able to approve a NADA for Clorsulon in about 6 months, an event that, under the Center's present policy, would result in termination of the emergency exemption for Albendazole.

Listed here are three alternative courses of action, together with the PROs and CONs of each option, that the Center might take in responding to recent developments in the regulation of Albendazole.

OPTION 1

The Center for Veterinary Medicine could permit the emergency investigational use of Albendazole to continue while implementing, as quickly as possible, the stronger drug distribution and monitoring controls proposed by the drug's sponsor at our August 13, 1984 meeting.

PRO

1. This option would continue the availability of an authorized drug to meet the still existent problem of liver fluke infections in cattle and sheep at least until a pending new animal drug application for a second flukicide is approved.

CON

1. We anticipate a delay of at least three months before additional controls can be put into place. During this time, consumers could continue to be exposed to residues from misuse of the drug that are not shown to be safe. Furthermore, it is quite possible that we could never

achieve the desired confidence that an unacceptably high incidence of misuse is not occurring with a drug that requires a 180-day withdrawal period.

2. This option is least protective of consumer safety.

OPTION 2

The Agency would immediately terminate the use and sale of Albendazole under the emergency authorization while the safety, analytical methodology, and distribution of the drug are discussed with SKAHP. Animals legally treated with the drug under the emergency authorizaton would be allowed to be slaughtered for food following observation of a 180-day withdrawal period.

PRO

1. This option would be most protective of human health.

2. The Agency would be doing what it said it would do if certain events occurred that have, in fact, come to pass.

CON

1. Because the existing foreign uses of Albendazole in both human and veterinary medicine, as well as anticipated domestic sales, are of great economic importance to SKAHP, the Center can expect a spirited and resource intensive struggle to ensue should we implement this option. Interest by producers, veterinarians and perhaps Congress would be brought to the Agency's attention.

OPTION 3

The Center would not terminate emergency investigational marketing of Albendazole until and unless our decision concerning the oncogenicity and "safe" levels of residues were affirmed in our appeals procedure, or by peer review by a panel of qualified scientists. We would work with SKAHP to implement additional controls as in Option 1 during the interim period.

PRO

1. Although we are confident that our scientists have reached the "correct" decisions on Albendazole under existing human food safety policy for animal drugs, this option would have the advantage of not depriving the sponsor of its legitimate property rights until all scientific issues are resolved.

CON

1. If this option were implemented, the drug's sponsor would have little incentive to seek a speedy resolution of the scientific issues involved while consumers would continue to be exposed to possibly unsafe residues.

RECOMMENDATION

The Associate Director for New Animal Drug Evaluation recommends that you terminate the emergency exemption for Albendazole as soon as possible. This decision will be strongly opposed by some, but it is entirely consistent with our original agreement with SEAMP and appears to be necessary in order to assure the safety of animal-derived food.

Terminating the exemption will mean that producers will be without an approved drug to treat liver flukes for a period of time. Another flukicide with a completed toxicology package indicating much less concern for food safety is close to approval, however, and, baring unforeseen problems, should be available in about 6-months.

FDA's regulations permit an investigational new animal drug exemption to be terminated immediately in the event of a danger to public health, with an opportunity for an informal hearing at a later time on whether the exemption should be reinstated (21 CFR 511.1(c)(4)). The Office of General Counsel has advised us that this procedure is applicable to termination of the emergency exemption.

Marvin A. Norcross, VMD

DECISION

OPTION 1

Approved__________Disapproved__________Date__________

Option 2

Approved*__________Disapproved__________Date__________

OPTION 3

Approved__________Disapproved__________Date__________

Attachments - TAB 1
TAB 2
TAB 3

Mr. Weiss. Did you order an immediate termination of this INAD in August 1984?

Dr. Crawford. Actually, what I did, Mr. Chairman, is that I had that recommendation reviewed by responsible officials in the Center, and I reached a conclusion at some time after that that it had to be concluded.

Mr. Weiss. Did you not call the president of the sponsor on September 13, 1984, to advise the company that the emergency use of albendazole would have to be terminated?

Dr. Crawford. I called the president twice. Once, to tell him that he would receive a letter and I wanted to be sure that he would be in town, and also to be on the lookout for a letter that I considered to be of utmost importance, and that I would like to receive a response back from him relative to the contents of that letter.

And I did receive a response back, and I called him again to tell him to be sure that he was going to receive then a second letter which indicated that the drug had to come off the market.

Mr. Weiss. When was that letter sent?

Dr. Crawford. I do not know. We can find out.

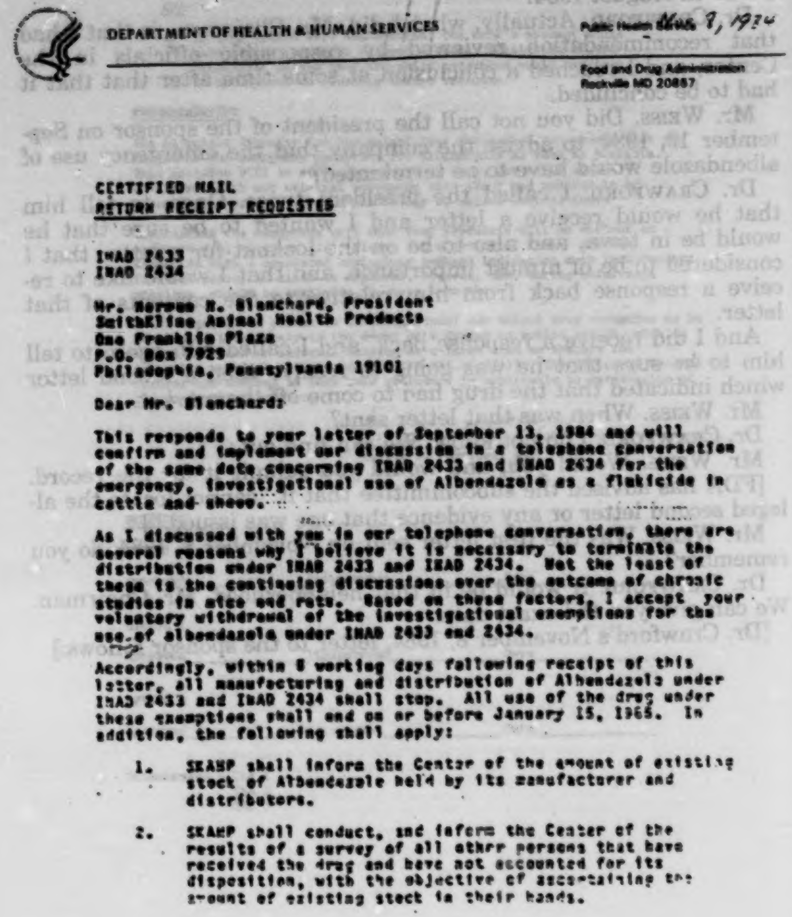
Mr. Weiss. Would you, and would you submit it for the record.

[FDA has advised the subcommittee that it "cannot locate the alleged second letter or any evidence that one was issued."]

Mr. Weiss. Was the first letter sent on November 8, 1984, do you remember?

Dr. Crawford. It would be in that neighborhood, Mr. Chairman. We can give you the exact date.

[Dr. Crawford's November 8, 1984, letter to the sponsor follows:]



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Nov. 7, 1984

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

INAD 2433
INAD 2434

Mr. Norman H. Blanchard, President
SmithKline Animal Health Products
One Franklin Plaza
P.O. Box 7929
Philadelphia, Pennsylvania 19101

Dear Mr. Blanchard:

This responds to your letter of September 13, 1984 and will confirm and implement our discussion in a telephone conversation of the same date concerning INAD 2433 and INAD 2434 for the emergency, investigational use of Albendazole as a flukicide in cattle and sheep.

As I discussed with you in our telephone conversation, there are several reasons why I believe it is necessary to terminate the distribution under INAD 2433 and INAD 2434. Not the least of these is the continuing discussions over the outcome of chronic studies in mice and rats. Based on these factors, I accept your voluntary withdrawal of the investigational exemptions for the use of albendazole under INAD 2433 and 2434.

Accordingly, within 8 working days following receipt of this letter, all manufacturing and distribution of Albendazole under INAD 2433 and INAD 2434 shall stop. All use of the drug under these exemptions shall end on or before January 15, 1985. In addition, the following shall apply:

1. SKAHP shall inform the Center of the amount of existing stock of Albendazole held by its manufacturer and distributors.

2. SKAHP shall conduct, and inform the Center of the results of a survey of all other persons that have received the drug and have not accounted for its disposition, with the objective of ascertaining the amount of existing stock in their hands.

Page Two - Mr. Norman H. [illegible]

3. SKAMP shall withdraw from the user level all unused supplies of the drug on or before January 15, 1985.

4. SKAMP shall promptly institute a monitoring system to ensure that consumers will not be exposed, due to drug misuse, to levels of residues above those shown to be safe. This system shall include a plan to contact those persons who have received Albendazole to advise them of the importance of complying with its authorized conditions of use and of the need to return to SKAMP treatment forms identifying owners of herds that were given the drug.

SKAMP should contact Dr. William Bisler, Associate Director for Surveillance and Compliance, Center for Veterinary Medicine, 5600 Fishers Lane, Rockville, Maryland 20857, in writing, within 10 working days indicating its acceptance of the above conditions and describing the details of its plan to ensure compliance with the authorized uses of Albendazole.

You will recall that this order is consistent with the conditions under which the emergency investigational use of Albendazole was authorized in letters from Mr. Gardner (FDA) to Mr. Ebright (SKAMP) dated October 1, 1977 and from me to Dr. Scott (SKAMP) dated December 14, 1979.

I am assuming SKAMP is waiving the right to a hearing under provisions of 21 CFR 511.1(c)(4) and 21 CFR Part 16. If this is not the case please let me know within 15 working days of receipt of this letter.

I appreciate the response you and the corporation have made with respect to Albendazole. Your willingness to market the compound under provisions of the emergency investigational use arrangement was a credit to SKAMP. Likewise, your attitude in the present circumstances is altogether commendable. Thank you.

If you have any questions concerning the contents of this letter please feel free to contact me at any time.

Sincerely yours,

Lester M. Crawford, DVM, PhD
Director, Center for
Veterinary Medicine

Mr. **Weiss**. So that is approximately 2 months after you had the conversation with the president of the sponsor telling him that emergency use of the drug had to be terminated?

Dr. **Crawford**. It would be within that neighborhood, yes.

Mr. **Weiss**. During your September 13, 1984, telephone conversation, did you agree to allow the sponsor to continue the albendazole program until such time as FDA had approved a substitute flukicide?

Dr. **Crawford**. No; I just discussed with him just the fact that the letter was coming.

Mr. **Weiss**. Did you prepare memoranda of this telephone conversation?

Dr. **Crawford**. No; there was no substance to the conversation, other than the letter itself, so I did not prepare a telecom.

Mr. **Weiss**. Did you not consider discussion with the president of the sponsor of the need to terminate use of albendazole to constitute a substantive conversation?

Dr. **Crawford**. All the substance was contained in the letter, so I did not feel that it required that.

Mr. **Weiss**. But your letter, you said, was sent 2 months after the fact, after that conversation?

Dr. **Crawford**. I would have to check those dates particularly, but I do not think that it would have been that long.

Mr. **Weiss**. Now we have a letter dated September 13, 1984, from Mr. Norman Blanchard, president of the sponsor, who refers to the telephone conversation of that date.

[The letter referred to follows:]

[illegible]

September 13, 1984

VIA AIRBORNE

Lester M. Crawford, D.V.M., Ph.D., HFV-1
Director
Center for Veterinary Medicine
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Doctor Crawford:

This letter confirms our telephone conversation of today's date regarding INAD #2433 and INAD #2434. SmithKline Animal Health Products commits to continue distribution of Albendazole under the emergency INAD until such time as the Fodd and Drug Administration approves a New Animal Drug Application for a substitute flukicide. Immediately upon notification by the Agency of such approval, we will voluntarily cease distribution of albendazole under the emergency INAD procedures.

I recommend that Dr. Guest and Mrs. Birkhead be assigned the responsibility of handling the procedures necessary to ensure that the commitment is met to have a product available to the livestock industry to control liver fluke infections.

As you know, we continue to pursue approval of our New Animal Drug Application supporting use of albendazole as a cattle and sheep anthelmintic in the United States.

Sincerely yours,

Norman H. Blanchard

Norman H. Blanchard

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1048A

Mr. **Weiss**. And without objection, I am going to read this paragraph to you:

"This letter confirms our telephone conversation of today's date regarding INAD No. 2433 and INAD No. 2434. SmithKline Animal Health Products commits to continue distribution of Albendazole under the emergency INAD until such time as the Food and Drug Administration approves a New Animal Drug Application for a substitute flukicide. Immediately upon notification by the Agency of such approval, we will voluntarily cease distribution of albendazole under the emergency INAD procedures."

Now does that refresh your recollection as to what that conversation was about?

Dr. **Crawford**. He was referring in the letter to a provision in the original approval, which indicated that there would be several potentials or several operant conditions which would require the removal of the emergency authorization.

One was, in fact, the approval of a new flukicide under a completely authorized NADA. The second was the distribution problems that we could document. And third was new toxicological information.

And in the letter of response, he chose to accept that particular article as one that he would comment on. Actually, albendazole was removed before a new flukicide was placed on the market, but not by very much.

Mr. **Weiss**. But again, the thrust of my questioning at this point concerns whether in that September 13 conversation you discussed with the president of the sponsor the necessity to terminate the use of albendazole, while agreeing that it could stay on the market until such time as a substitute drug was approved.

Dr. **Crawford**. I did not discuss anything except the fact that the letter would contain the position of the FDA.

Mr. **Weiss**. Well again, I do not want to repeat the paragraph which I read to you, but it is quite clear that Mr. Blanchard writes, "This letter confirms our telephone conversation of today's date," regarding the continued use and eventual termination of the albendazole INAD.

Do you have any explanation as to why you think that he had that impression concerning your discussion?

Dr. **Crawford**. No; he may just be saying that this confirms that we had a telephone conversation, but that is the only explanation that I can give.

Mr. **Weiss**. Why do you think that the sponsor in letters dated September 13 and November 21, 1984, states that you did agree on September 13 to allow albendazole to stay on the market until an alternative drug has been approved?

[The sponsor's September 13 letter to FDA is in the record; the sponsor's November 21, 1984, letter to FDA follows:]

One Franklin Plaza, P.O. Box 7929, Philadelphia, Pennsylvania

SmithKline Beckman
CORPORATION

Norman H. Blanchard
President, SmithKline Animal Health Products
(215) 751-7081

Rec'd in HFV-123
4a

November 21, 1984

orig only

Certified Mail/RRR

Dr. Lester M. Crawford, Director (HFV-1)
Center for Veterinary Medicine
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: INAD 2433 and INAD 2434
Your Letter Received November 14, 1984

Dear Dr. Crawford:

This acknowledges receipt of your letter date stamped November 8th, 1984 and received by us November 14th, 1984 concerning INAD 2433 and INAD 2434 for the emergency, investigational use of Albendazole as a flukicide in cattle and sheep as authorized by the Center for Veterinary Medicine in December, 1979.

I reconfirm our commitment to voluntarily cease distribution of Albendazole under the emergency INAD, as agreed upon in our telephone conversation of September 13, 1984, and as outlined in my letter to you of the same date.

Following our telephone conversation of September 13th, I instructed Norden Labortories to cease the manufacture of Albendazole with the exception of lots then in progress. Accordingly, the last lot of Albendazole suspension (Lot #S1859) was completed on October 19, 1984, and the last lot of Albendazole paste (Lot #S1852) was completed on October 23, 1984, and arrangements have been made to return base drug inventory to its source.

With respect to the specific points raised in your letter, we propose to proceed as follows:

1. SKAHP will inform the CVM of the amount of existing stock in Norden and its branch warehouses as of Friday, November 30th. There is no outside manufacturer or distributor as Norden invoices and ships direct to veterinarians.
2. SKAHP will conduct a survey to determine the amount of Albendazole stock existing in the hands of veterinarians and will issue a report to the CVM as of Friday, December 30, 1984.

3. SKAHP is prepared to initiate withdrawal of Albendazole from veterinarians as of January 15, 1985, assuming that another flukicide will have received an NADA by that date. However, we feel that withdrawal of the drug from the user level is unwarranted and would cause interruption of the availability of a flukicide to cattle and sheep producers. With increased efforts to assure compliance with the withdrawal period, and other requirements of the INAD's, consumers will not be exposed to residues above the levels shown to be safe. Our experience indicates that it will take two to three months for the manufacturer of an approved flukicide to manufacture, test and distribute the product to the user level. During this time, it is important that Albendazole remain available to meet the need for an effective flukicide in states where liver fluke is a critical problem.

4. We believe that a monitoring system is already in place. However, as discussed in your office in August with Mr. Hinnah of Norden Laboratories, we agreed to tighten the monitoring of treatment forms through the office of Ms. Helen Birkhead of SKAHP's Applebrook Research Center. However, in response to the request in your letter received November 14th, 1984, we agree to advise veterinarians again of the importance of complying with the authorized conditions for the use of Albendazole and the need to return to SKAHP treatment forms identifying owners of herds that were given the drug.

We respectfully request that you contact your associates in the Center for Veterinary Medicine with respect to our intentions as stated in this letter. I can advise you that we do not anticipate exercising our administrative rights; however, we prefer not to waive the right to a hearing under the provisions of 21 CFR 511.1(c)4 and 21 CFR Part 16.

Please be assured that we fully intend to abide by our previous commitment to cease distribution of Albendazole. I believe we have acted in good faith, and look forward to your continued collaboration. We will continue to seek approval of the New Animal Drug Application for Albendazole.

Yours sincerely,

Norman H. Blanchard

Norman H. Blanchard

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Dr. CRAWFORD. I do not know.

Mr. WEISS. Did you specifically correct the firm's misimpression that it could continue albendazole's emergency use until FDA had approved an alternative drug?

Dr. CRAWFORD. There are additional letters in the file relative to that. Yes. If I may, may I take the liberty of reading the response?

Mr. WEISS. Of course. Give me the date of the letter.

Dr. CRAWFORD. November 8, 1984.

Mr. WEISS. Go ahead.

Dr. CRAWFORD. "This responds to your letter of September 13," which I believe is the one that you are talking about. "As I discussed with you in our telephone conversation, there are several reasons why I believe it is necessary to terminate distribution of INAD 2433."

And then these reasons were, "Not the least of these is the continuing discussions over the outcome of chronic studies in mice or rats. Based on these factors, I accept your voluntary withdrawal of the investigational exemptions for the use of albendazole."

[Dr. Crawford's November 8, 1984, letter to the sponsor is in the record.]

So that was our attempt at correcting the situation in terms of his interpretation of why it was coming off the market.

Mr. WEISS. Dr. Crawford, stop right there. You say at the start of that very letter: "This responds to your letter of September 13, 1984 and will confirm and implement our discussion in a telephone conversation of the same date concerning INAD 2433 and INAD 2434 for the emergency, investigational use of albendazole * * *." Then it says, "As I discussed with you in our telephone conversation, there are several reasons why I believe that it is necessary to terminate the distribution * * * under INAD 2433 and INAD 2434."

So you did discuss termination with him in that September 13 telephone call, right?

Dr. CRAWFORD. Yes; I told him that the letter had to do with albendazole, and that it was very important, and that it regarded termination. And that he should read the letter and respond. His response, you have read to some extent. Then on December 20, if I may continue.

Mr. WEISS. Please, go ahead.

Dr. CRAWFORD. I wrote him again. And item 2 in that letter was, "Our agreement on your voluntary recall of albendazole cannot be contingent upon approval of any other INAD's for a flukistat or flukicide. Furthermore, we do not agree that the recall should be limited to veterinarians. Your voluntary recall of albendazole should be to the user level," et cetera.

[Dr. Crawford's Dec. 20, 1984, letter to the sponsor follows:]

DEC 20 1984

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

RE: INAD 2433
INAD 2434

Mr. Norman H. Blanchard, President
SmithKline Animal Health Products
One Franklin Plaza
P. O. Box 7929
Philadelphia, Pennsylvania 10101

Dear Mr. Blanchard:

This acknowledges receipt of your letter dated November 21, 1984. We have reviewed your response to my November 8, 1984, letter with these conclusions:

1. Your reference to a monitoring system already in place is inadequate in that your monitoring system has failed to control the distribution of albendazole within the context of the investigational exemptions and the requirements of 21 CFR Part 511. We agree that you should advise veterinarians of their responsibilities, but that alone does not constitute adequate monitoring. We request that you advise us in detail how your monitoring will be adequately strengthened until outstanding stocks are recalled. This applies to all outstanding INAD's for albendazole.

2. Our agreement on your voluntary recall of albendazole cannot be contingent upon approval of any other NADA for a flukistat or flukicide. Furthermore, we do not agree that recall should be limited to veterinarians. Your voluntary recall of albendazole should be to the user level, which may necessitate subrecalls by your direct accounts. Your recall plan should be developed in consultation with our Kansas City District office and action and completion dates should be established..

3. We intend to recommend seizure actions against lots of albendazole outside the INAD exemption and any lots not promptly returned after you initiate recall by January 15, 1985.

4. We request that you voluntarily terminate all ongoing albendazole INAD's immediately. Otherwise, pursuant to 21 CFR 511.1(d) and 21 CFR Part 16, you have the right to request a hearing. Our review of the

files and the findings of field investigations indicate that the distribution of albendazole under the investigational exemptions is out of control.

I request that you respond to this letter with your plans within 10 days of receipt directly to Dr. William B. Bixler, Acting Associate Director for Surveillance and Compliance (HFV-200), Center for Veterinary Medicine, 5600 Fishers Lane, Rockville, Maryland 20857. His office will be your contact for handling these issues as I advised you in my earlier letter.

Sincerely yours,

Lester M. Crawford, DVM, PhD
Director, Center for
Veterinary Medicine

cc: HFV-1
HFV-2
HFV-100
HFV-230
HFV-236
HFV-234
HFC-20
GCF-1(Geyer)
HFR-3100
HFR-7100
HFV-16(Doc.Unit)
Initialed:SBGuest:12/18/84
EBallitch:km:12/19/84

Dr. **Crawford.** But it was not contingent upon an approval of another flukistat, as we corrected.

Mr. **Weiss.** Why did you wait more than 3 months from the time that you received the September 13, 1984, letter to December 20, 1984, to correct the firm's misimpression?

Dr. **Crawford.** Well, we had ongoing correspondence, as you can see. And we were correcting it all along. I agree, Mr. Chairman, that the most emphatic correction was not until December 20. But I think that you will agree that in the November 8 letter that the reason listed as the outcome of chronic studies in mice and rats and no other reason. We believed that that was sufficient correction, although it is more emphatic on December 20.

Mr. **Weiss.** Dr. Settepani, on October 1, 1984, I understand that you wrote the first draft of what became Dr. Crawford's November 8, 1984, letter to SmithKline. Is that correct?

Dr. **Settepani.** That is correct, sir.

[The draft referred to follows:]

October 1, 1984

INAD 2433
INAD 2434

Norman E. Blanchard, President
SmithKline Animal Health Products
One Franklin Plaza
P.O. Box 7929
Philadelphia, Pennsylvania 19101

Dear Mr. Blanchard:

This responds to your letter of September 13 and will confirm and implement our discussion in a telephone conversation of the same date concerning INAD 2433 and INAD 2434 for the emergency, investigational use of Albendazole as a flukicide in cattle and sheep.

I am, pursuant to 21 CFR 511.1(c)(4), ordering withdrawal of investigational exemptions previously granted to SmithKline Animal Health Products under INAD 2433 and INAD 2434.

This action is being taken on the basis of data submitted to the Center demonstrating that Albendazole caused a significant increase in malignant sarcomas in female mice and in male and female rats together with the fact that no regulatory method exists for detecting residues of the drug in animal-derived, human food at levels associated with a calculated one in one million lifetime increase in the risk of cancer. In addition, we have ~~recently learned of the existence~~ documented instance of significant misuse of Albendazole, i.e., use that is outside the conditions authorized under the emergency INADs, that could result in the exposure of consumers to levels of residues that are not demonstrated to be safe.

¶ Based on these fac I have decided, ~~therefore~~, that the continued authorization of widespread emergency use of Albendazole in food-producing animals would be inconsistent with the public health. Accordingly, within 5 working days following receipt of this letter, all manufacturing and distribution of Albendazole under INAD 2433 and INAD 2434 ~~will~~ shall stop.

I would remind you that this order is consistent with the conditions under which the emergency investigational use of Albendazole was authorized in letters from Mr. Gardner (FDA) to Mr. Ebright (SKAHP) dated October 1, 1979 and from me to Dr. Scott (SKAHP) dated December 10, 1979.

In accordance with the provisions of section 512 of the Act (21 U.S.C. 360b) you have a right to a hearing on whether the investigational exemption that I have terminated should be reinstated. Should you wish to avail yourself of an opportunity for a hearing, you must file with the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, a written appearance requesting a hearing by November 15, 1984. Such appearance must give reasons why the investigational exemption's should be reinstated.

The Center's scientists have concluded that conformance with the conditions of use of Albendazole under all of the existing INADs (including those INADs for emergency use) will result in residues in established human food that are below those shown to be safe. Also, animals treated under the more limited non-emergency INADs must be identified as experimental animals when presented for slaughter and, in other ways, are under much stricter control than are animals given Albendazole under the two emergency INADs. For these reasons, I am limiting my order to withdraw investigational exemption to INAD 2433 and INAD 2434 at this time.

Based in part upon the facts presented in the preceeding paragraph and in part, because of the economic disruption to the meat producing industry that might result if the early effective date of the ban on the manufacture and distribution of Albendazole were also applied to the actual use of the drug in cattle and sheep, I am prepared to delay the effective date for terminating use of the drug until January 15, 1985, provided you agree to the following conditions:

1. You will inform the Center of the amount of existing stock of Albendazole held by its manufacturer. and distributors

2. You will conduct, and inform the Center of the results of, a survey of veterinarians that have received the drug and have not accounted for its disposition, with the objective of ascertaining the amount of existing stock in their hands.

3. You will ~~recall~~ withdraw all unused supplies of the drug on or before January 15, 1985.

4. You institute a monitoring system to ensure that consumers will not be exposed to levels of residues above those shown to be safe due to drug misuse between now and January 15, 1985. This system should include a plan to contact veterinarians who have received Albendazole to advise them of the importance of complying with its authorized conditions of use and with the need to return to you treatment forms identifying owners of herds that were given the drug.

You should contact Dr. William Bixler, Associate Director of Compliance, in writing, within 14 days indicating your acceptance of the above conditions and describing the details of your plan to ensure compliance with the authorized uses of Albendazole.

If you have any questions concerning the contents of this letter please feel free to contact me at anytime.

Sincerly yours,

Lester M. Crawford, DVM, PhD
Director, Center for
Veterinary Medicine

Mr. **Weiss**. Now your draft states that the Center for Veterinary Medicine was "prepared to delay the effective date for terminating use of the drug until January 15, 1985 * * *." Why did you select that date?

Dr. **Settepani**. When I received the incoming letter to prepare a draft response to, there was a page of handwritten instructions from Dr. Guest as to the basics that the letter should say, and that was one of the dates that was in that draft from Dr. Guest.

Mr. Weiss. Dr. Crawford, in that November 8, 1984, letter, you advised the sponsor in writing that albendazole would have to be removed from the market, but not until January 15, 1985. Why did you select that particular date?

Dr. Crawford. We believed based on information that we had from the field and other sources that there was probably that amount of product in distribution, and that it would not be possible to get it all off the market until that particular date, or approximately that time.

We wanted the firm, as you know, Mr. Chairman, to cease manufacture as soon as possible, and then to put in place a hard and fast plan for removing it from the marketplace. We had to select a date. I think that you will agree that we could not have said November 15 or any time quite like that. Because at the time of that letter, I believe that the product was still in manufacture. That had to stop first.

And then we had to give them some date where it could no longer be there at all. And January 15 was our best estimate of what was the most appropriate time.

Mr. Weiss. By mid-August, FDA had already found the drug to be a carcinogen. Could you not have asked the manufacturer at that point to recall the drug that was already in distribution?

Dr. Crawford. Well, we received that recommendation from Dr. Norcross, as you mentioned, later after he had had a chance to review the Cancer Assessment Committee report. Keep in mind that the Cancer Assessment Committee is a committee of individuals that are empowered to look upon request at questions of carcinogenicity. They make the recommendation to the Associate Director, who is required to review their conclusions in an appropriate manner, and then make an appropriate recommendation to me, which he did, and I reviewed the recommendation myself.

We wanted to be sure that we agreed with those conclusions, and we did. Although I must admit that your line of questioning is completely appropriate. It does seem like a long time, and it does seem a little bit like bureaucracy. But it is about as quick as we can do the thing and still be consistent with proper review and normal operating procedures.

Mr. Weiss. Well, as a matter of fact, is it not true that you authorized and, in essence, directed the company to keep albendazole on the market until a substitute drug was ready for distribution? Is that not the case?

Dr. Crawford. No, that is in the letter. We say that that is not the case.

Mr. Weiss. On October 3, 1984, Merck Sharpe & Dohme met with FDA to discuss the "reasonableness of achieving [the] goal" of approving their flukicide, clorsulon, "by January 15, 1985," on an accelerated schedule.

[FDA's memorandum of that meeting follows:]

MEMORANDUM OF CONFERENCE

Date of Conference: October 3, 1984

Subject: Clorsulon, NADA 136-742

Between: Merck Sharp & Dohme Research Laboratories

Bruce A. Halley
Anthony Lu
Kenneth G. Davis
Robert J. Nessel
Don Griffin
Dennis Wallace

and

FDA/CVM

A. R. Gabuten, D.V.M., HFV-135
John Olsen, Ph.D., HFV-135
John Matheson, HFV-152
Ted Farber, Ph.D., HFV-150
Gloria Hicks, HFV-142
Donald Gable, D.V.M., HFV-130
Marvin Norcross, V.M.D., Ph.D., HFV-100
Richard Carnevale, V.M.D., HFV-100
Joseph Settepani, Ph.D., HFV-102
Robert Livingston, Ph.D., HFV-140

The meeting was held to discuss the following:

1. Goal - An approved flukicide.

2. Objective: Reasonableness of achieving goal by January 15, 1985.

	HFV-130/135	Target Dates
1.	Labeling Text	November 1, 1984
2.	FOI - tentative final	November 15, 1984
3.	Approval Package (minus EIAR)	November 15, 1984

	HFV-140/142	Target Dates
1.	Review Manufacturing	
	Changes completed	October 10, 1984
	Resolve questions if necessary.	November 1, 1984
2.	Assay validation for dosage form, if validation, post approval.	______
	HFV-140/144/146	
1.	Comparative Metabolism	
	Merck submits	October 31, 1984
	HFV-140/144 review	November 15, 1984
2.	Method Validation	
	Paper review	October 10, 1984
	Merck submits tissue (request for)	November 1, 1984
	Validation completed	December 1, 1984
	HFV-150/152	
1.	V. P. (Vapor Pressure)	
	Merck submits data	November 1, 1984
2.	Biodegradation (soil and water)	
	Merck submits data	______
	HFV-150/152 review	______
	Protocols for item No. 2 oral comments from HFV-152.	Within 5 days.

		Target Dates
3.	Incomplete items in June 14, 1984 letter.	
	Merck response	November 1, 1984
	HFV-150/152 review	December 1, 1984
4.	EIAR	
	Merck submits	___________
	HFV-150/152 review	___________

The tentative target dates were agreed upon by all concerned.

Adriano R. Gabuten
Adriano R. Gabuten, D.V.M.

Mr. **Weiss**. Was January 15, 1985, chosen because that was the date that the albendazole emergency INAD was slated for termination?

Dr. **Crawford**. No. We knew at that time, we had received an earlier request, as you may know, from Merck regarding clorsulon to place it on an emergency authorization just as was albendazole. We rejected that petition sometime earlier. They continued to work toward the approval of clorsulon, and I do not know what their internal goals were. But I suspect that they would have been earlier than FDA's goals for ultimate approval.

We continued to have meetings with them at the appropriate level relative to the approvability of their product. Now let me say parenthetically that our experiences with allowing the emergency use of albendazole, as I mentioned earlier, were uncomfortable.

We would rather have a drug approved or not approved. We do not like to deal in those gray areas, and that is obvious since we have never done that before or since. And we did not want to have a situation where we would be forced into considering another emergency approval of a drug like clorsulon.

We wanted very much if the drug was approvable, and that is to say safe and effective, to get it on the market without very much overlap. There was some overlap when there was no fluke drug available. But we did not want to have it happen again as it did in 1979.

Mr. **Weiss**. Mr. Matheson, we are going to direct some questions to you. Would you identify yourself, and describe what your responsibilities are.

Mr. **Matheson**. Yes, sir. My name is John Matheson. I am chief of the environmental staff of CVM. I am also the focal point for the FDA for National Environmental Policy Act concerns.

Mr. **Weiss**. The microphone is not very sensitive, so if you would pull it closer to you, I think that it will help.

Were you present at the October 3, 1984, meeting with Merck?

Mr. **Matheson**. Yes, sir, I was.

Mr. **Weiss**. Were there plans around that time to coordinate clorsulon's approval with albendazole's withdrawal?

Mr. **Matheson**. At the meeting of October 3, there was a timetable prepared on the bulletin board or on the blackboard which did aim toward approval of the product by the end of January 1985. I do not recall any linkage or discussion about albendazole, however.

Mr. **Weiss**. And do you remember who presided at that premeeting on October 3, 1984?

Mr. **Matheson**. I believe that was Dr. Gable.

Mr. **Weiss**. And do you recall whether Dr. Gable suggested at that time that clorsulon's approval would be coordinated with albendazole's withdrawal?

Mr. **Matheson**. No, sir, I do not recall specifically that he said that.

Mr. **Weiss**. He may not have said it specifically, but did you get the impression that such coordination was being planned?

Mr. **Matheson**. I did have that impression; yes, sir.

Mr. **Weiss**. Thank you.

Dr. Zeeman, would you identify yourself, and tell us what your responsibilities are.

Dr. **Zeeman**. My name is Maurice Zeeman. I work for Mr. Matheson. I am a toxicologist on the environmental staff. I have been there about 5 years. And my job is that I am assigned a variety of environmental concerns, from reviewing environmental impact statements to participating in surveillance and compliance activities such as withdrawals. I also peer review scientific articles, actively participate in contracts and research.

I would say that by far my major responsibilities involve review of environmental materials for preclearance of new animal drugs.

Mr. **Weiss**. Were you involved in the environmental review of clorsulon?

Dr. **Zeeman**. Yes, I was.

Mr. **Weiss**. On September 7, 1984, a few days before Dr. Crawford called SmithKline concerning termination of the albendazole program, didn't you attend a meeting at which Dr. Crawford expressed a strong desire to speed the approval process for clorsulon in light of the need to remove albendazole from the market?

Dr. **Zeeman**. I attended a meeting on that date, yes.

Mr. **Weiss**. And do you recall Dr. Crawford expressing a desire to speed the approval process for clorsulon in light of the need to remove albendazole from the market?

Dr. **Zeeman**. The meeting was to discuss the status of clorsulon.

Mr. **Weiss**. Right.

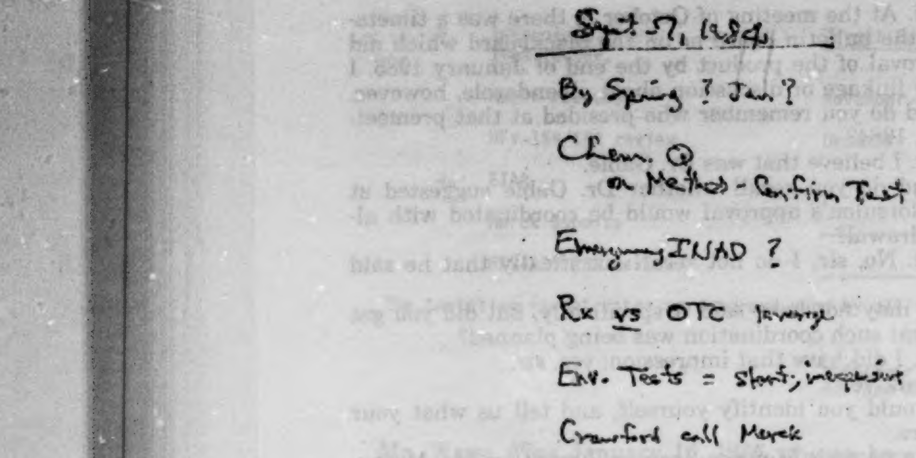
Dr. **Zeeman**. To find out how far along we were internally in relation to the approval of that drug. I do not remember a direct conversation from Dr. Crawford linking albendazole in any way. But the impression was generally there that there was a problem with albendazole, and what could we do to solve that problem.

Mr. **Weiss**. And do you recall discussions about clorsulon being put on the fast track?

Dr. **Zeeman**. Yes.

Mr. **Weiss**. From your notes of that meeting, do you recall that Dr. Crawford agreed to call Merck?

[The notes referred to follow:]



Sept. 7, 1984

By Spring ? Jan ?

Chem. Q
on Methods - Confirm Test

Emergency INAD ?

Rx vs OTC leverage

Env. Tests = short; inexpensive

Crawford call Merck

Dr. Zeeman. Yes. I have a note to that fact.

Mr. Weiss. What was to be the purpose of that call?

Dr. Zeeman. To discuss the status of the drug at their end. That was my understanding.

Mr. Weiss. To discuss? Say it again?

Dr. Zeeman. The status of the drug at their end.

Mr. Weiss. Of clorsulon?

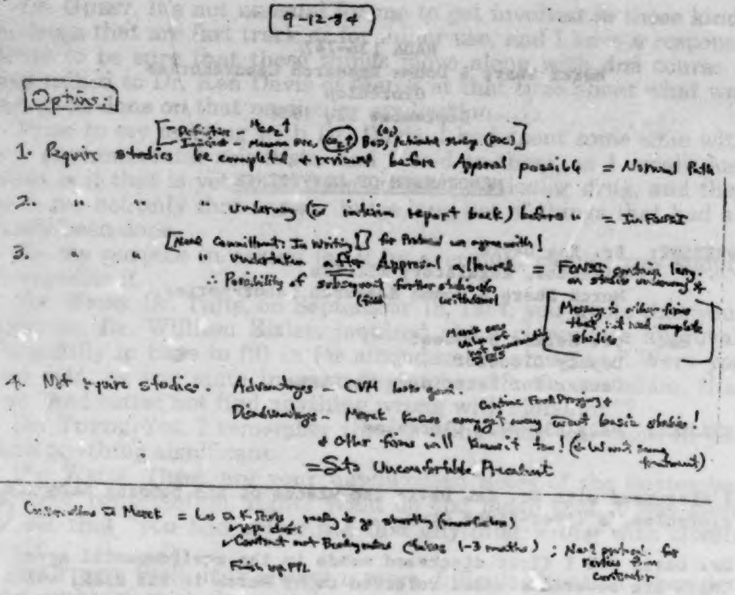
Dr. Zeeman. Yes.

Mr. Weiss. And was it also supposed to involve discussion of what FDA thought needed to be done to secure an approval for the drug?

Dr. Zeeman. That was not my impression.

Mr. Weiss. Dr. Crawford, you called SmithKline concerning the termination of the albendazole on September 13, 1984. According to Dr. Zeeman's notes of an internal meeting the day before, you had called a Merck official and learned that the firm was "ready to go shortly on manufacturing clorsulon."

[The notes referred to follow:]



9-12-84

Options:

[- Definition - ↑CO2↑ - Indirect - Measure dose, (CO2↑) BOD, Activated sludge (DOC)]

1. Require studies be completed + reviewed before Approval possible = Normal Path

2. " " " underway (or interim report back) before " = In Force

[Need Commitment: In Writing] for Protocol we agree with!

3. " " " undertaken after Approval allowed = FONSI pending long. on studies underway &

∴ Possibility of subsequent further studies & (full withdrawal

Merck sees value of not [illegible] EIS

[Message to other firms that it need complete studies]

4. Not require studies. Advantages - CVH lets go!.

Disadvantages - Merck knows they got away w/out basic studies! Continue Field Progress &

& other firms will know it too! (& will want same treatment)

= Sets Uncomfortable Precedent

Conversation w Merck = Lab & K-Study ready to go shortly (manufacture) large dose

✓ Contract not finalized (takes 1-3 months) ; Need protocol for review from contractor

Finish up FTL

Mr. **Weiss**. Did you write a memorandum of the conversation you had with Merck?

Dr. **Crawford**. I don't recall whether I did or not. I will have to check.

Mr. **Weiss**. Would you?

Dr. **Crawford**. Yes, I will.

Mr. **Weiss**. And if you have such a memorandum, would you submit that for the record?

Dr. **Crawford**. I certainly will, Mr. Chairman.

[FDA has advised the subcommittee that "No memorandum was prepared."]

Mr. **Weiss**. Dr. Guest, on September 12, 1984, you met with a Merck representative and requested a protocol for a needed environmental study by "overnight carrier" so that it could be reviewed "quickly." Why were you in such a rush?

[Dr. Guest's memorandum of that meeting follows:]

NADA 136-742
Merck Sharp & Dohme Research Laboratories
Clorsulon
September 12, 1984

MEMORANDUM OF CONFERENCE

PRESENT: Dr. Ken Davis
Director, Regulatory Affairs
Merck Sharp & Dohme Research Laboratories

and Dr. Gerald B. Guest
Deputy Director
Center for Veterinary Medicine

SUBJECT: NADA 136-742, Clorsulon

I discussed with Dr. Ken Davis the status of his pending NADA for clorsulon, a liver-fluke drug.

Dr. Davis and I first discussed needs in the environmental area. There are several studies referred to by Merck in the EIAR, which have not been submitted. CVM needs these. The biodegradation study is needed. I asked Dr. Davis to quickly submit a protocol by overnight carrier and we will review quickly so that study can get underway. Dr. Davis indicated that Merck will contract outside of Merck for that study. I indicated to Dr. Davis that if that study had not reached an endpoint by the time all other aspects of the application are finished and if there are no overriding circumstances, that we could go ahead based on a commitment to complete the work after approval.

Other items pending include at least the FOI summary, submission of trials on comparative metabolism, labeling, and method validation. I asked Dr. Davis to contact Dr. Norcross to set-up a meeting to discuss all "loose ends" and to chart the course for completing these items. Dr. Davis said he would do so.

Gerald B. Guest
Gerald B. Guest, DVM

cc: Dup, HFV-16
Dr. Crawford, HFV-1
Dr. Norcross, HFV-100
Dr. Gable, HFV-130
Dr. Gabuten, HFV-135
Dr. Livingston, HFV-140
Dr. Farber, HFV-150
Mr. Matheson, HFV-152

GBGuest:mk:9/19/84

Dr. **Guest**. It's not unusual for me to get involved in those kinds of drugs that are fast track or for minor use, and I have a responsibility to be sure that those things move along with due course. I had talked to Dr. Ken Davis of Merck at that time about what was left to be done on that particular application.

Prior to my meeting with Dr. Davis, I had spent some time with our environmental scientists, and I said to them, as I recall, just what is it that is yet to be done on that particular drug, and they gave me not only that answer but a long list of things that had already been done.

So, my purpose in asking for it by overnight carrier was simply to expedite it.

Mr. **Weiss**. Dr. Tufts, on September 18, 1984, you wrote that your superior, Dr. William Bixler, inquired about clorsulon's approval: "hopefully in time to fill in for albendazole's phaseout." Were you also told, as you state in your September 18 memorandum, that you "had better not find anything wrong with clorsulon"?

Dr. **Tufts**. Yes, I remember that. I think that was more in jest than anything significant.

Mr. **Weiss**. These are your handwritten notes of the September 18, 1984, conversation, right? What do you mean that it was more in jest that "you had better not find anything wrong with clorsulon"?

Dr. **Tufts**. Well, it is always a more difficult situation when you find problems with drugs that are moving along in their examination or review track, and it is a much happier situation if we do not run into problems. And, so, I did not attach anything in particular significance to that in my mind.

Mr. **Weiss**. Immediately following the line, "We had better not find anything wrong with clorsulon," your September 18 notes state: "Dr. Crawford would be furious as it had to serve as a substitute for albendazole."

[Dr. Tufts' September 18, 1984, memorandum, part of which was crossed out before it was delivered to the subcommittee, follows:]

To: File
Fm: NRT
RE: Clorsulon (Merck)/albendazole (SKF)

Sept. 18, 1984

Dr. Guest c/o 8:30 a.m. questioning me about my interest in clorsulon, a flukicide (Merck) undergoing review for approval, hopefully in time to fill in for albendazole's phase-out.

Dr. Guest had three concerns:

1. We had better not find anything wrong with Clorsulon [illegible], as it had to serve as a substitute for albendazole.

2. Why didn't we do an inspection of Clorsulon before this? (I replied that I had found out about the drug only yesterday, and had immediately begun to track it down to ascertain its status).

3. Why did we decide to inspect this study? Do we inspect all submitted data sources? (No - only particular drug entities such as "fast track" (expedited review") which Clorsulon was. And we had not seen a notice of trial, and thus did not know about Clorsulon)

-2- (Clorsulon)

4. Human Food Safety had reviewed the data in support of Clorsulon and had pronounced it o.k. What was I doing with it? (I had read some of the meeting/review report and three things bothered me: higher incidence of Ca in male rats on high dose v.s. controls (yet the drug was not held responsible); various hyperplasias said not to be pre-tumorous; prior inspection of the contract lab (Dawson) seemed to me to reveal ~~[illegible]~~ a botched teratology study (NOT SO AS [illegible]," there-fore, I felt we should check this out more thoroughly, particularly in light of the Albendazole experience; and I was unhappy with the decision to cut corners in the approval process.

5. But why inspect Clorsulon at this late date? (Having just become aware of this drug, we yet had ample time to do a data audit and either resolve any questions about the drug or perform further tests if needed. And "fast track" drugs were to be subject to GLP/data audit inspections (policy).

6. Right after lunch, Dr. Brisker stopped me in the corridor again re: Clorsulon. Why had we not inspected the Clorsulon study before now? I

* Ms. Pourell was also present there.

brought him to my office* and showed him a 1982 "Fast track drug list" from DE (Dr. Dahle), xerox copy, barely legible. There was a faint, barely visible notation about Merck, Sharp and Dohme and an illegible number, but no mention of the name Clorsulon (We later found Clorsulon was initially tested as MK-40 not as Clorsulon) The list had been xeroxed from a yellow legal tablet in pencil and the number hadn't reproduced and the name was lacking. A new employee had not noticed the entry (nor would most of us, either), and the 1982 list was filed after the available data had been processed. So, to all intents and purposes, we had not seen a Clorsulon notice of trial nor a nonclinical study — until now. So, we immediately set to work, and we are awaiting a copy of the Final Report and protocol before issuing a data audit assignment to EDRO on Clorsulon at Dawson Laboratories.

"Hold everything until you hear from me," said Dr. Bixler. "Do not send anything out on Clorsulon until or unless you hear from me."

He then left the office.

Mr. **Weiss**. Now, that does not sound like a jest to me.

Dr. **Tufts**. Well, it was said in a jesting way.

Mr. **Weiss**. You mean the very first item that you put on this memorandum is an item said in jest. Is that what you are telling us? Would you look at this memorandum?

[Pause.]

Dr. **Tufts**. Sir, I think we have to go back to the context within which this was written.

Mr. **Weiss**. Go ahead.

Dr. **Tufts**. And that is that it is obvious to all of us, or it was at the time that with a phaseout of a drug like albendazole without a substitute, there would be an enormous problem due to the vacuum thereby created. And I think it was just common knowledge that we needed something to be able to fill in with to attenuate such a situation.

I think the common knowledge is reason enough to make such a comment.

Mr. **Weiss**. Well, common knowledge, indeed, may be reason enough, but it is hardly a joking matter, is it?

Dr. **Tufts**. Well, at the time it was a jest.

Mr. **Weiss**. Well, would you point out some other jokes in that memorandum for us?

Dr. **Tufts**. I had not intended to write jokes. I simply was recording the conversation as I remembered it, sir.

Mr. **Weiss**. Thank you.

Dr. Settepani, did you have any food safety concerns regarding the agency's review of clorsulon?

Dr. **Settepani**. I had concerns about the approval and about the review that the jacket had received before it was approved, yes, sir.

Mr. **Weiss**. Would you tell us what your food safety concerns were regarding the agency's review of clorsulon?

Dr. **Settepani**. Yes, sir, I will try. I would characterize them though as concerns with the approval package. I received the approval package in my office on February 13, and I read through it to look for areas where either the administrative record was not clear, whether there were omissions, whether the correct scientific expertise had been brought to bear on all of the issues and all of the studies and that is my normal job to do that.

Mr. **Weiss**. Right.

Dr. **Settepani**. And I wrote a memorandum that listed five or so of those concerns. Shall I go over them?

Mr. **Weiss**. Would you please spell out what the food safety concerns were? You are talking about your memorandum dated March 20, 1985. Is that correct?

Dr. **Settepani**. Yes, sir.

[The memorandum referred to follows:]

Chem

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Date March 20, 1985

From Joseph A. Settepani, Ph.D. JAS
(HFV-102)

Subject Approval of NADA 136-742 for Clorsulon in Cattle

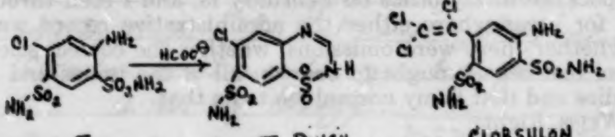
To Mervin A. Norcross, VMD
(HFV-100)

I cannot concur with approval of NADA 136-742 for the use of clorsulon as a flukicide in cattle at this time for the following reasons:

1. There is no memorandum from Dr. Barnes to support statements in the FOI summary that the regulatory analytical method for residues met our standards for such assays in the hands of FDA and USDA chemists. I cannot recall any NADA being approved without such a memorandum in the approval package of a drug requiring a withdrawal period.

2. I do not concur with approval of an NADA about which a substantial question exists concerning its effect on the environment. Dr. Colaianne's memorandum of January 22, states that "some degree of phytotoxicity (i.e., reduction in shoot weight) was detectable even at the lowest dose level (1 mg/kg) of clorsulon tested". One mg/kg approximates the concentration of the drug in urine and feces of treated cattle. What will we do if even lower levels of drug are found to exhibit phytotoxicity now that the drug is approved?

3. Chlorodisulfamoylaniline (I) is a key intermediate in the preparation of a large family of diuretic agents that includes chlorothiazide (trade name: Diuril) (II). Thiazides are formed from I by reaction with acylating agents and the reaction I to II almost surely occurs in vivo. The structural resemblence of clorsulon to I is obvious. These facts, which should have been revealed by the sponsor, make many of the questions in Dr. Weber's memorandum of January 10, 1985, very much to the point. I believe these questions should have been addressed by the drug's sponsor before approval of their NADA.



I   II DIURIL   CLORSULON

4. The no effect level in the 14-week dog study was raised from an original assignment of 2 mg/kg to 8 mg/kg with very little explanation in the record (i.e., no discussion of the histological results on which the 2 mg/kg NOEL was based). I could find no discussion of the fact that this dog study - which is critical because it was used to establish the tolerance for residues of the drug - was conducted using 3 dogs/sex/group whereas our guideline calls for 4 dogs/sex/group for a valid study. Apparently, our reviewers were not provided with an opportunity to approve protocols for the 90-day studies. Did these studies fall short of our guideline requirements in other ways?

I am concerned that the requested evaluation of the rat feeding study with clorsulon by the Center's CAC was not carried out. The report of a September 15, 1984 meeting at which the decision was made not to have a CAC review does not provide very many details of this decision. Statistically significant kidney epithelial hyperplasia in treated rats was judged to be not pre-neoplastic. A statistically significant increased incidence of kidney tubular adenoma and adenocarcinoma in treated male rats was judged to be not drug related based on historical control data and (unspecified) literature data. Apparently, there was no examination of this data by a Center statistician. No FDA pathologist evaluated or participated in the discussion of the rat study according to the written record. There is no indication that the positive results in genetic toxicity studies were considered in the evaluation of the rat feeding study. This study would appear to meet the criteria proposed by Dr. Farber for a "for cause" quality control examination of histological slides by an FDA pathologist.

I want to emphasize that I have no quarrel with the conclusions of any of the scientists who evaluated the submitted studies on clorsulon. I have not looked at this data myself. My only concern is that the written record provided in the evaluating memoranda do not explain the basis for the decisions that were made and do not indicate that the appropriate disciplines, especially statisticians and pathologists, were involved in these decisions.

I notice that Taylor Madill has declined to sign off on this approval because of the likelihood that the drug will be used "off the label" in lactating dairy cows. I understand that Merck scientists presented a talk on the efficacy of clorsulon to control liver flukes in this production class at a recent Eastern States Veterinary Conference attended by Dr. Carnevale. It has not been our policy to require an analytical method for residues in milk for drugs approved in beef cattle. From a food safety viewpoint, I would not like to see any drug used in dairy cows until the Center has established a withholding period for milk from treated cows. Nevertheless, our Extra Label Drug Use Policy permits this off label use if a veterinarian is involved in a client-veterinarian relationship and no approved drug is available to accomplish the therapeutic effect.

In my opinion, this is not sufficiently protective of human health. Accordingly, I propose that we amend the Center's Extra Label Drug Use Policy to disallow the use of drugs in lactating dairy cows unless they are approved in that production class, or the Center has data on which to base a milk withholding period for the drug and is in possession of a regulatory method of analysis for residues in milk to monitor observance of that withholding period. I also believe we should have a regulatory program to monitor for residues in milk drugs such as flukicides that the states do not look for in their monitoring programs.

cc: HFA-16 (2) NADA 136-742 Dup. Trip.
HFV-101
HFV-102 (3)
HFV-201
HFV-230 (TMadill)
R/D:JASettepani:jvp:3/19/85
F/T:jvp:3/20/85

Mr. WEISS. Tell us what your food safety concerns were.

Dr. SETTEPANI. Well, the first thing that was missing from the package was a memorandum from our chemist in charge of validating the analytical method, and that was not in there. And when I questioned him about that, he said that he had given his oral assurance, but I would like to see a complete approval package before I concur with it and I like to see things in writing.

The next question was that there were substantial questions concerning its effect on the environment. Dr. Colaianne had stated, he is our biostatistician, that there was some degree of phytotoxicity detectable even at the lowest level of clorsulon tested, and at the time I thought that that approximated the concentration of a drug in excreta. I since found out that there may be higher levels of the drug in excreta. And I was concerned that we did not have a no effect level. I generally like to see no effect levels demonstrated so that we know what we are dealing with.

Also, there had been a—I found a memorandum in the record from Dr. Weber dated January 10, 1985, in which he asked many questions concerning the metabolism of the drug. Those questions were not answered in the administrative record. Actually, in the memorandum, it was agreed that FDA would conduct some research to answer those questions, and I felt that those questions should have been answered by the sponsor before we approved the drug.

[The memorandum referred to follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Date January 10, 1985

From Residue Evaluation Branch, HFV-144

Subject Clorsulon, Response to December 4, 1984 Metabolism Questions

To Antiparisitic & Physiological Drugs Branch, HFV-135
ATTN: Dr. Gabuten

NEW ANIMAL DRUG APPLICATION NO. 136-742 (015)
Submission dated December 19, 1984

1. Introduction

This submission is in response to a meeting that was held with the sponsor's representatives on December 4, 1984.

In that meeting several problems involving the comparative metabolism and metabolism studies of clorsulon were discussed with the sponsor's representatives. Although we tried to characterise some of our concerns at that meeting, the sponsor's submission dated December 19, 1984 simplified the concerns down to two: 1) Do we have any residue assay experiment that was done in the absence of scavenger which would demonstrate the stability of residues? 2) Do we think the rat toxicology model is an appropriate model for human safety assessment in the case of MK-401? In attempting to respond to these questions the sponsor's scientists submitted the results of three experiments which they believe answer these questions. However, we believe that the sponsor's representative has not quite characterised the nature of our questions regarding clorsulon comparative metabolism. Our concern was not only the stability of residues per se, but the reactive nature of the residue which the sponsor in numerous places of their previous submissions had alluded to. These concerns also arose from chromatograms showing that unprotected beef liver extracts gave rise to a multitude of transformation products and very little parent compound. The sponsor has repeatedly demonstrated and/or stated that the parent compound comprises the principle if not the only extractable metabolite in edible tissues of cattle as well as in rat tissues. Our concern as stated in that conference was to point out that a myriad of transformation products may occur in mastigated tissue in the human stomach as opposed to the rather stable residue profile as seen in a unhomogenized or chemically protected steer liver or kidney. Our second major concern was that if the large amounts of non-polar products were the case in actual practice, then what evidence does the sponsor have that the rat produced significant amounts of the non-polar biotransformation products.

SPONSOR'S SUBMISSION:

The sponsor has submitted three studies which they have included in previous submissions. The first study is Stability of Clorsulon in Tissue

(Study CA-173), from report entitled "Clorsulon (MK-0401): Study in Cattle (CA-173 and CA-187) to Provide a Method of Analyses in Tissue for Residue and to Determine Residues in Animals Dosed at 10 mg/kg with an Oral Suspension," J. W. Wood, Jr. and F. P. Baylis, 10/28/83 in NADA submission, 12/27/83.

This experiment according to the sponsor was one in which tissue samples stood at room temperature for a period of 5 days. Neither hydroxylamine or parent drug was added to the assay. Tissues were analyzed by the sponsor's original (CH_3I)/GC method. The results showed an average ratio before and after standing was approximately 1.02. This according to the sponsor indicates that there was virtually no degradation of the residues during that time period. However, we note that this result is in question since we understand that the method does not homogenize the tissue until the time of analysis. We believe this does not answer our general concern about the stability of the residue in homogenized tissue. Our conclusion is that the study does not answer the question of non-polar product formation in homogenized tissue.

The second study is Stability of Clorsulon Residues in Cattle Kidney, Muscle and Comparison of Assays by LC/UV Method with Assays by CH_3I/GC Method (CA-173 and CA-187), from report entitled "Clorsulon (MK-0401): Study in Cattle (CA-173 and CA-187) to provide a Method of Analysis in Tissue for Residue and to Determine Residues in Animals Dosed at 10 mg/kg with an Oral Suspension," J.S. Wood, JR. and F.P. Baylis, 8/7/84 in Supplementary NADA submission, 9/10/84. The essence of this experiment is 1) to demonstrate stability of MK-401 residue in tissue after a period of 10 months between assays, and 2) to demonstrate the essential equivalence of the two assay methods, that is, the earlier GC method and the newer LC method. A total of 26 kidney samples were compared and a ratio of LC to GC methods was approximatley 1.06. Six muscle samples were also compared by the same two methods resulting in an average ratio of 1.11. The sponsor claims that these studies show the essential equivalence of the two methods as well as the stability of the drug residues between drug assays. They further point out that since the earlier method does not employ any protective reagent the close agreement between these results demonstrate the stability of residues in tissue. We believe that this study was not designed to answer the question that has been posed. The tissue conditions (intact storage) were not those which would permit the degradation of residues. It would appear that the tissue was stored in an unhomogenized and frozen condition that would not permit those reactions to occur.

The third study the sponsor has submitted is entitled Unaltered ^{14}C-MK-0401 in Kidney and Liver Tissues of Steer and Rats from "Comparative Metabolic Disposition of C-MK-0104 in Kidney and Liver Tissue of One Day Post Dose Steer (No. 3456, Expt. CA-193) and Rats (Expt. ADM-49)," S. H. L. CHIU, 10/30/84, Supplementary NADA submission 11/2/84.

In this study rat tissue of experiment ADM-49 was assayed by combustion of a tissue water homogenate (1:4). The sponsor states that after these residue assays were made, the homogenate samples were stored at -20 C for 4 months before they were used in an reverse isotope dilution assay (RIDA) experiment for the parent drug. The results of the RIDA experiment showed that the kidney and liver to contain 82% and 79% of the parent drug, respectively. The sponsor goes on to point out that since the extractable residue in the one-day kidney and liver tissues was 88 and 89%, respectively of the total residues, the maximal possible percent side reactions that might have occurred or otherwise be due to metabolites would range from 6% in the kidney to 10% in the liver. What is not said in this discussion, however, is the length of time that these tissues were exposed or left at 37 C or some other temperature and for what length of time prior to freezing. Undoubtedly the amount of reaction that might take place should be both temperature and time dependent. We also note that this experiment was not conducted in cattle tissues which is somewhat questionable as to its applicability.

In the sponsor's next to last paragraph of their letter they go on to state that MK-401 undergoes conversion to non-polar products in tissue extract experiments with organic solvents; however, when tissue was handled in aqueous solution or in storage, the residue was stable and did not exhibit degradation problems. They go on to suggest that these reactions are likely to occur in the organic phase of tissue extracts whereas the results of their experiments suggest that it does not happen in vivo. We take exception to these conclusions since it would appear that cattle tissue was not examined nor was a controlled experiment with time conducted using edible cattle tissues. The sponsor points out that side reactions of reactive amines have been reported in the literature and aldehyde conjugates specifically are mentioned in a recent report by Dayton in Drug Metabolism Disposition, 8, 230 (1980). This paper by Dr. Dayton is particularly interesting because it suggests that the reaction between amines and aldehydes occurs in vivo and is not necessarily and should not be attributed to the reaction caused by contamination of solvents with acids or aldehydes. The second paper by Bosin, et al. Anal. Biochem. 128, 287-293 (1983), deals with the same problems of cyclization of amine containing compounds in tissue homogenates. In this case rat platelets were examined for their ability to cyclise an indole compound to a tetrahydrobetacarboline. After removal of formaldehyde from the organic solvents, the cyclization of the compound was still observed and research indicated that the formaldehyde was in fact being generated from the tissue preparation itself. These results tend to support our concern that tissue components are capable of forming aldehydes which can react with MK-401 to produce the non-polar transformation products. It is also apparent that if this were the case that addition products should form in the tissue. However, since they do not, this may be a case where the residue partitions into a part of the tissue (e.g. membrane) that does not contain a significant concentration of aldehydes.

The sponsor's research report concluded by suggesting that there is no indication that the tissue residue of MK-401 would degrade without a lengthy organic solvent treatment such as used in extraction procedures and purification. They go on to suggest that because the same residue patterns exist in cattle and rat and the stability of the residue having been demonstrated in the above experiments there should be little doubt that the rat is a good model for human food safety.

CONCLUSIONS:

1. The studies in general did not address the principle scientific questions at issue: 1) will residues of MK-401 form significant amounts of non-polar products in macerated edible tissue of treated cattle and 2) what evidence do we have that rats were exposed to significant amounts of these products.

2. As noted in the above review, the tissues involved were either not macerated or they were homogenized in the case of the rat and not cattle, and were stored in the frozen conditions for 4 months. The rat study did not give details of the sample preparation or conditions (time, temperature) from which one could conclude that the non-polar products would not readily form in a homogenate under in-vivo conditions.

3. The sponsor's comparative metabolism study in male rats offers little assurance that the rat was exposed to significant amounts of the non-polar transformation products. The agency did not have the opportunity to comment on the protocol and it was not conducted according to our general guideline recommendations. From the amounts of non-polar products seen in hydroxyalamine treated rat kidney and liver tissue, it would appear that not more than 1 or 2% of these metabolites are present in rat tissues as the result of a single dose.

We would have recommended that the rats of both sexes be administered the drug and that the dosing be continuous for five to seven days. Furthermore, we would have recommended that urine and feces be examined initially for metabolite profiles. If the latter step had been done, especially by using a trapping agent like hydroyxlamine, we would have a better understanding of the exposure to rats with the non-polar transformation products in terms of the total administered drug.

The current comparative metabolism guideline requirement have been substantially met by the sponsor's studies. They have shown that using the same tissue treatment extraction and purification steps, virtually identical comparative metabolism profiles are exhibited by steers and rats. In this case, almost all extractable residue was parent compound with evidence of some non-polar metabolites contributing no more than about 1 to 3% of the residue in the chromatograms. The point at issue is that in order to demonstrate these profiles, a chemical fixative was used to prevent reaction of the parent compound with aldehyde that may be present in the tissues or the solvents. On the other hand, if the fixative treatment had not been used on either rat or steer tissue, then the picture may also have been very similar but in that case may have shown complex metabolism as in the case of the unprotected steer liver profile. We believe that this situation has revealed an issue not discussed in the present metabolism guideline. This is: What is the residue metabolite profile in macerated tissue or after the tissue is ingested? Thus, the issue of what humans are exposed to is still open. We intend to do experiments on the generic question of metabolite profiles and how they may change upon ingestion. These studies will initially involve clorsulon since the question has arisen with this compound. Upon completion of the planned experiment, our guidelines may require modification to anticipate the possibility of tissue degradation of residues. Of equal importance will be the adequacy of the toxicological studies in laboratory test species and ways to assess new or dramatically different residue compositions in human food (as ingested) compared to the in vivo exposure to laboratory species.

4. An initial study that should be done is to take cattle liver and kidney and fortify with MK-401 parent drug. These tissues should then be homogenized and kept under conditions to simulate the stomach and intestinal tract. This experiment should be run using hydroxylamine to stop side reactions and should be run for times up to 6 hours (see attached protocol). In addition, rat feces and urine should be checked for parent drug after administering the drug for 5 to 7 days to determine the amount of parent drug and non-polar metabolites.

Nicholas E. Weber

Nicholas E. Weber, Ph.D.

Attachment
cc: HFV-16(2)
HFV-130
HFV-140(3)
HFV-150
t/d:12-28-84:tlc:NEWeber
t/f:01-10-85:tlc:NEWeber
Initial:Livingston

MK-401 Stability Protocol

1. Obtain fresh cattle liver, slice into 1" thick slices and pack in ice for transport to laboratory.

2. Make 1 to 3 homogenate of tissue to buffer (1 part tissue + 3 parts buffer) at 37 C pH 1 with HCl. Make second homogenate pH 7 with NaOH if needed. Use at least 50 grams tissue in each case taken from composite of all lobes of liver (not just edge of one lobe).

3. Place 20 ml aliquot (equivalent to 5 grams tissue) in 50 ml beaker for each sample and place in 37 C water bath with shaking.

4. Add MK-401 equivalent to 3 ppm to each beaker.

5. Stop reaction by adding solid hydroxylamine and ammonia. Extract with etnyl acetate and continue with assay.

6. a) Run the following time points in duplicate 0, 1, 3, 6 hours (8 samples).
   b) + reagent blank (no tissue) ± hydroxylamine
   c) + spiked tissue minus hydroxylamine

Mr. WEISS. What were those questions?

Dr. SETTEPANI. Oh, I do not have his memorandum here, sir, and I—it had to do with removing some metabolites from concern.

Mr. WEISS. Did you have any additional food safety concerns?

Dr. SETTEPANI. Yes, sir. I had a question concerning a no-effect level in the 14-week dog study. It was originally assigned by the toxicology reviewer as 2 milligrams per kilogram and then it was raised by another subsequent memorandum by the reviewer's supervisor to 8 milligrams per kilogram, and there was very little explanation in the record of that.

The firm had in the meantime submitted additional information, but I generally do not read the data. I do not try to second guess the toxicologists. All I ask is that the toxicologist's memorandum constitute a complete basis for the decisions that they reach, and I did not see any basis for the raising of the no-effect level.

And then I found a memorandum again in the toxicology evaluation package that the reviewer had asked for a review by the Center's Cancer Assessment Committee. There was a statistically significant increase in kidney epithelial hyperplasia, and there was a statistically significant increase in kidney tubular adenomas and adenocarcinomas. Those were limited to the male rats. And the reviewer suggested that those be evaluated by the Cancer Assessment Committee.

[The memorandum referred to follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandu

September 21, 1983

Division of Toxicology/BVM, HFV-330

MK-401

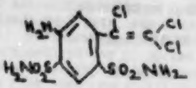
Cancer Assessment Committee

I. Trade Name: MK-401 (L-631,529)

Chemical Name: 4-amino-6(trichlorethenyl) 1,3 benzenedisulfonamide

Class of Compound: sulfonamide

Structure:



Molecular Weight: 380.66

Empirical Formula: $C_8 H_8 Cl_3 N_3 O_4 S_2$

Purity: 98% as determined by HPLC assay and TLC

Proposed Use: Cattle Fasiolicide

II. Use in Target Animals:

Proposed Use: Cattle fasiolicide

Route of administration: Oral suspension, by drench

Dose: Not to exceed 15 mg/kg/body wt as a single dose

Proposed withdrawal time: 28 days

II. Efficacy of Oral MK-401 Against Fasciola hepatica in Cattle:

To establish the optimum effective oral dose of MK-401 against Fasciola hepatica in cattle, seven randomized trials were conducted at 3, 6 or 12 mg/kg dose levels against cattle induced with flukes. In each trial, the cattle were necropsied 20-30 day after treatment and the liver, gall bladder and main bile ducts were examined for flukes.

Results: The dose response to MK-401 was found to be linear up to 23 mg/kg for eight-week old flukes and linear up to 4.5 mg/kg for fourteen-week old flukes.

The dose of 7 mg/kg was selected as the recommended therapeutic dose based on the predicted percent efficacies for the fitted dose response functions.

III. Chronic Toxicity/Carcinogenicity Studies on MK-401

LIFETIME ORAL CARCINOGENICITY STUDY IN MICE:

Species/Strain: Mice/Crl-CD-1.

No. of Animals/Sex/Dose: 50.

Age at the Beginning of Experiment: 4-5 weeks.

Intended Dose: 0, 0, 0(control), 50, 150, 450 mg/kg/day.

Calculated dose: 0, 0, 0(control), 44, 120, 306 ug/kg/day

Vehicle: 0.5% aqueous methylcellulose suspension

Route of Administration: Oral intubation.

Total Duration of Dosing: 92-121 weeks.

Study Termination Schedule: In Weeks

High dose males	92
Low dose males	93
Mid dose males	95
Low dose females	118
Mid and high dose females	121

Histomorphological examination:

This included evaluation of all tissues from control I and high dosage group (450 mg/kg/day) of mice. Histomorphology examination of remaining groups was limited to tissues with gross changes and urinary bladders.

Results:

The details of each physical, biochemical or hematological observation and treatment-related effects have been previously reviewed and described in an initial DT review dated October 6, 1982. No physical signs were attributable to treatment. Drug-treatment did not affect in body weight gain except for mid-dose treated females who had significant decrease in weight gain. A number of male mice developed preputial abscesses and ear infections which were treated with Achromycin antibiotic ointment (3%). Hematological examination was unremarkable. Biochemical observations were also unremarkable. Hematology values were not significantly different between the control and treated animals. No significant differences were observed with respect to the tumor types between the control and the treated animals.

Based on the data presented by the sponsor, DT concluded that MK-401 is not carcinogenic in mice since there was no treatment related neoplasia or hyperplasia. No salivary gland or urinary bladder tumors were observed in this study. These conclusions are reaffirmed here and the no effect level is set to 306 mg/kg.

Lifetime Carcinogenicity Study in Rats Following In Utero Exposure - MK-401:

Background:

The initial review (memorandum dated October 6, 1982) of three-month oral toxicity study of MK-401 in rats at 2, 20 and 100 mg/kg/day dose levels demonstrated several microscopic changes. These changes included salivary gland neoplasia in 3 rats, two from the 2 mg and one from 20 mg/kg/day dose level. Furthermore, the hyperplastic foci in the urinary bladder epithelia were noticed the at 20 and 100 mg dose levels. In a subsequent 14-week oral toxicity study at a dose of 55 mg/kg salivary gland neoplasms were also seen comparable to those of the initial study. The urinary bladder hyperplasia of the epithelium was not observed in the second study. In order to clarify these findings, a 54-week chronic toxicity and lifetime carcinogenicity studies were initiated. Summaries of these studies, other than the lifetime study, are summarized later in this memorandum.

Performing Laboratory: Dawson Research Corporation, Orlando, Florida.

Species/Strain: Rat/Charles River-CD-COBS.

No. of Animals/Sex/Group: 50.

Dose Levels: Intended - 0, 0 (control), 5, 20, 80 mg/kg.
Actual - 0 (control), 3.8, 12.6, 48.8 mg/kg.

Vehicle: 0.5% methylcellulose suspension.

Route of Administration: Oral, by gavage.

Length of Exposure:

14 days prior to breeding, through gestation and lactation and later for 122 weeks (males) and 125-126 weeks (females), Total duration of study was 29 months.

Observations:

Individual and mean body weight, physical signs, hematology, serum biochemistry, animals dead or sacrificed with primary neoplasms, time of onset of confirmed neoplasms, histomorphology.

Results:

1. Treatment with MK-401 had no significant effect on body weight.

2. No ophthalmologic effects were attributed to drug treatment.

3. Some of the clinical signs such as facial staining, alopecia, swollen eyelids, swollen ears and feet, ulcerations, pilorection, dacryorrhea, inactivity, loss of balance, labored breathing, preputial discharge and swelling were observed in both treated and control rats and were not considered to be treatment related.

Lower abdomen hair staining was observed in both male and female rats treated with the high dose as well as with the mid dose in male rats only.

4. The incidence of mortality was approximately twice that of control in the high dose treated male animals at 18 and 24 months of age. The sponsor concluded that treatment with MK-401 had no apparent effect on the incidence of mortality based on the low incidence of deaths observed during the 12 to 18 month period and the overall mortality at the time of termination of the study. No explanation was provided for the significantly higher mortality observed during the 18 to 24 month period of the study.

5. The periodical clinical hematology and serum biochemical analyses showed no treatment-related changes.

6. The sponsor claimed that histomorphological examination showed no increased incidence of benign or malignant neoplasia in drug treated rats and acknowledged only a significant increasing trend in the incidence of kidney pelvic epithelial cell hyperplasia in female rats at 20 and 80 mg/kg dose levels. Furthermore, the sponsor considered this effect as secondary to the pelvic lesions such as pyelitis of infectious origin, pelvic calculi, and pelvic mineralization. However, review of the histopathological data by DT (October 6, 1982) found that the incidence

of kidney tubular adenoma together with adenocarcinoma was higher in the high dose males than in the pooled controls, and that there was an apparent increase in kidney epithelia hyperplasia in female rats at the mid and high dose levels. The bone marrow hyperplasia, salivary gland carcinomas and the urinary bladder hyperplasia reported in the 54-week rat toxicity study were not apparent in the present study.

The sponsor submitted the historical control data from the performing laboratory and from their own laboratory on the incidence of tubular adenoma and adenocarcinoma in the same rat strain used in these studies and argued that the incidence of these tumors was not significant. Furthermore, the sponsor also argued that the hyperplasia of the kidney epithelial tissue in female rats is secondary to other accompanying renal pelvic changes commonly seen in rats at that age, and therefore, is not drug-related. Rereview of the lifetime carcinogenicity study in rats following in utero exposure of MK-401 confirms the previous concerns expressed by DT (Review dated October 6, 1982). The historical control data is attached for the CAC review. The following tables derived from the sponsor's data on the incidence of kidney tumors are included for the information of the CAC.

Summary of kidney tumors and other effects - Life-time Carcinogenicity Study in Rats following *in utero* Exposure to MK-401

· Female Rats

				mg/kg/day (actual)		
Tumor type/groups	0	0	0	5(3.8)	20(12.8)	80(48.8)
Tubular adenoma	1/50	0/49	0/50	0/50	0/50	0/50
Tubular adenocarcinoma	1/50	0/49	0/50	0/50	0/50	0/50
Pelvic epithelium, hyperplasia	2/50	3/49	2/50	1/50	8/50	9/50
Hydronephrosis	2/50	3/49	3/50	2/50	6/50	7/50

Summary of Kidney Tumors and other effects - Life-time Carcinogenicity Study in Rats following in utero Exposure to MK-401.

Male Rats

				mg/kg/day (actual)		
Tumor type/groups	0	0	0	5(3.8)	20(12.8)	80(48.8)
Tubular adenoma	1/50	1/5	0/50	1/50	0/50	3/50
Tubular adenocarcinoma	1/50	0/51	0/50	0/50	0/50	1/50
Pelvic-transitional cell carcinoma	0/50	0/51	0/50	0/50	0/50	1/50
Pelvic-epithelial hyperplasia	7/50	3/51	3/50	5/50	10/50	4/50
pelvic-squamous cell metaplasia	0/50	0/51	0/50	0/50	0/50	2/50
Hydronephrosis	1/50	2/51	2/50	4/50	3/50	9/50

Methods of Statistical Analysis Used

The firm used the Mantel-Haenszel procedure which compares the entire life-table adjusted curves for the high dose and control groups, taking into account time to tumor and time to death without tumor. This was done for individual palpable tumor occurrences and the results cumulated over time. Results for tumor sites with fewer than 6 animals with tumors were evaluated using an exact procedure and adjustments to the P-values were made for the multiplicity of tumor sites examined. The results for kidney epithelial hyperplasia were evaluated by a trend test that measures the progressiveness of hyperplasias with increase in dose (including the controls = zero dose). Adjustments were made for multiplicity of comparisons of individual doses with controls.

Conclusions:

1) Female Rats -

There was a statistically significant trend for progressiveness of kidney epithelial hyperplasia with an increase in dose. Individual dose comparisons vs. controls showed statistically significant increases for the mid-dose (20mg/kg/day) group (p=0.013) and for the high dose (80 mg/kg/day) group (P=0.011).

2) Male Rats - The comparison of controls vs. the high dose group showed that the occurrence of kidney tubular adenoma was statistically significant (P = 016). No statistically significant evidence of an increase in kidney epithelial hyperplasia was observed except for the mid dose group (P=0.015), The firm claims that this may be a fortuitous result, since there was no evidence of a trend.

IV Summaries of other Submitted Toxicity Studies:

DT has reviewed (memorandum dated October 6, 1982) the toxicological data in support of MK-401 and assigned no effect levels for each of the following relevant studies.

Acute Toxicity in Mice and Rats:

Species	Sex	Route	LD_{50} (mg/kg)
Mouse	M	Oral	>20,000
	F		
Mouse	M	IP	678
	F	IP	761
Rat	M	Oral	>10,000
	F		
Rat	M	IP	938
	F	IP	845

Twenty-Nine Day Day Oral Range Finding Study in Dogs:

Results:

At dose levels of 100 mg and over, tremors, ataxia, anorexia, decreased activity, dehydration and loss of body weight were observed. The severity of these symtoms was dose dependent. Furthermore, hematological effects included leucopenia, lowered platelet and erythrocyte counts, decreased hematocrit and hemoglobin concentration. Several changes in biochemical parameters also occurred at the higher dose levels which included a transient increase in serum BUN, creatinine, glucose, SGPT, SGOT and alkaline phosphatase levels. Urinalysis revealed an increased number of renal epithelial cells, leucocytes and the presence of occult blood at the higher dose levels.

Gross histopathological examination showed scattered focal hemorrhages in the heart, kidney lungs, lymph nodes and GI tract at the 300 and 900 mg dose levels.

Conclusion:

Based on the hematological, biochemical and gross histopathological changes observed in this study, DT set the limit of 5.0 mg/kg as the NEL.

Thirty-One Day Oral Range Finding Study in Rats - L-631,529(TT # 75-056-0).

Results:

1. Salivation was observed at all dose levels.

2. Treatment - related decrease in body weight gain was observed in male rats at the 300 and 900 mg/kg/day dose levels throughout the study. There were no treatment-related changes in body weights of female rats at any dose level.

3. Serum alkaline phosphatase activity was significantly increased in male rats treated at the 300 mg/kg/day dose level. At the highest dose level, alkaline phosphatase activity was increased in both sexes. No other enzyme data was reported by the sponsor.

Conclusion:

DT considered that the study was adequately performed and based upon the data, 100 mg/kg dose level was set as the NEL.

Fourteen-Week Oral Toxicity Study in Dogs:

Results:

1. There was a transient slight loss of body weight observed among the high dose levels which was attributed to the insufficient amount of food availability rather than drug administration.

2. No treatment-related hematological changes were observed except for two dogs which showed abnormal hematology. The hematological abnormalties included decreased RBC, hemoglobin, hematocrit, leucocyte and platelet counts, and increased prothrombin time.

3. The sponsor claimed that no drug-related biochemical changes were observed. However, a spontaneous increase in serum SGPT levels was observed in one dog administered 2 mg/kg/day dose at 13th week of treatment.

Furthermore serum T_4 concentrations measured by the UpJohn Diagnostic Laboratory in male dogs treated with the 2, and 32 mg dose showed a decrease in drug weeks 4 and 8 while Dr. Siegel's Laboratory, The University of Pennsylvania, School of Veterinary Medicine reported an increase in Serum T_4 values.

4. Gross morphological examination was carried out after the animals had received 2, 8 and 32 mg/kg/day dose levels for 94 or 95 days. No gross-morphological changes were attributed to drug-treatment. Absolute as well as relative thyroid weights were significantly decreased in male and female dogs treated with 8 and 32 mg/kg/day dosage groups. The sponsor claimed that the changes in thyroid weights are biologically insignificant since there was no apparent effect on Serum T_4 levels.

5. The postmortem examination revealed no treatment-related gross changes. At 32 mg dose level focal prostatic hyperplasia was observed in one dog and nodular hyperplasia was present in spleens of two dogs, one each at 8 and 32 mg dose levels respectively.

Conclusion:

DT concurred with the sponsor that the changes in relative organ weights (thyroid and liver) and the splenic hyperplasia are not drug-treatment related. DT agreed with the interpretation of the sponsor since similar changes were not found in a subsequent dog study in which a higher dose level (55 mg/kg) of MK-401 was used. DT set the no effect level as 8 mg/kg/day based on a neutropenia seen in some dogs at 32 and 55 mg/kg/day.

Fourteen Week Oral Toxicity Study in Dogs:

Purpose:

This study was undertaken to determine whether changes observed in absolute liver weights and absolute and relative thyroid weights in the previous 90 day dog study are drug-treatment-related.

Results:

There were no drug-related changes in the following parameters with some exceptions for individual dogs as outlined below:

No drug-induced EKG changes were observed. Ophthalmological examination was unremarkable. Two treated dogs showed abnormal hematology when sacrificed at the fifth week of drug treatment. The abnormal hematology included decreased RBC, Hgb, Hct; leucocytes platelets, and prothrombin time. The other dog had a decrease in WBC and total and differential counts. No adverse biochemical changes occurred except in one animal sacrificed during the fifth week of the study. This animal had elevated SGOT, SGPT, alkaline phosphatase, bilirubin, BUN, creatinine, and K^+, and decreased glucose, albumin, total protein, Na^+ and Cl^-. Serum T_4 levels were significantly increased in the treated animals at 4 weeks of drug treatment, but were comparable to the controls at 8 and 13 weeks.

Conclusion:

The changes in liver and thyroid weights as well as other adverse effects were not observed in this high dose study as seen in the previous dog study. DT set 8 mg/kg as the no effect level for the dog based upon neutropenia.

Thirteen and Fourteen Week Oral Toxicity and 13 Week In Utero Exposure Studies in Rats:

After reviewing all three subchronic rat studies, the question of increased level of alkaline phosphatase activity at 300 mg/kg was not resolved, therefore, DT set the NEL to 30 mg/kg for these studies.

Reproduction Study - The Female Rat:

Unremarkable effects seen at 5, 20 or 80 mg dose levels.

Mouse Teratology Study:

An increased incidence of pseudopolydactyly of both forepaws occurred at high (50 mg) dose level. A slight increase in the rate of resorptions was observed at the high dose level. Based upon the questionable significance of postaxial pseudopolydactyly, the NEL was set to 10 mg/kg.

Teratological Evaluation in Rabbits:

Unremarkable effects were observed, therefore, DT set the highest dose of 50 mg/kg as the NEL.

Fifty-four Week Chronic Toxicity in the Rat:

DT pointed out an increased incidence of pancreatic acinar atrophy, degeneration of the pancreas and myocardial degeneration and bone marrow hyperplasia at the high dose level. The sponsor was requested to reexamine the slides of the questioned tissues. The sponsor responded (letter of July 15, 1983) by providing the data from two independent pathologist's, one from sponsor's laboratory (Dr. C.P. Peter) and other from the private consultant (Dr. R.A. Squires, Squires and Asso. Inc. Ruxton, MD). The sponsor claims that there are no treatment-related effects in either the heart, pancreas, or bone marrow in the 54-week chronic toxicity study in rats with MK-401. The following tables are derived from the data of the sponsor's pathologist and from the independent consultant hired by the sponsor.

Data from Sponsor's Pathologist (Dr. Peter)

Tissue	Sex	Dose (mg/kg)				
		Control I	Control II	5	20	80
Pancreas						
No. Examined						
Acinar atrophy	F	3/25	0/25	0/25	2/25	7/25
	M	7/25	8/25	1/25	1/25	6/25
Chronic degeneration	F	1/25	1/25	0/25	3/25	3/25
	M	3/25	2/25	2/25	0/25	5/25
Heart						
Chronic degeneration	F	1/25	1/25	2/25	0/24	1/25
	M	5/2	2/25	2/25	6/25	6/25
Bone Marrow						
Hyperplasia	F	1/25	1/25	1/25	1/23	1/25
	M	6/25	2/24	16/24	6/24	3/25

Results:

The incidence of changes was similar in all treatment groups including controls and the changes were considered incidental and not related to drug-treatment.

Data from Dr. Squire, Robert A. Squire Asso. Inc., Ruxton, MD.

Tissue	Sex	Dose (mg/kg) 0	Control	5	20	80
Pancreas						
Total lesions	F	6/25	9/25	5/26	4/24	7/25
	M	8/25	11/25	13/25	7/25	15/25
Heart						
Total lesions	F	4/25	4/25	5/26	0/24	3/25
	M	11/25	8/25	8/25	12/25	12/25

Results:

Dr. Squire reported that no unusual lesions either in the pancreata or hearts were observed which could be dose dependent. The tissue alterations are common in the aging rat population and no apparent compound related trend or incidence of severity could be observed. Dr. Squire did not examine bone marrow slides.

Conclusion:

After reviewing the data submitted by the sponsor, DT agreed with the sponsor's conclusion that the changes observed in pancreata, heart and bone marrow were not related to drug-treatment (memorandum dated Sept. 6, 1983). One cause for concern was that the high incidence of bone marrow hyperplasia observed in male rats at 5 mg dose level. However, the life-time carcinogenicity study in rats did not reveal bone marrow hyperplasia related to drug-treatment.

DT raises the following concerns and seeks advice from the CAC:

1. The biological significance of the kidney tumors observed in male and female rats at the mid and high dose levels need clarification from the CAC.

B.R. Sonawane

B.R. Sonawane, Ph.D.

Judith W. Hauswirth

Group Leader

cc: HFV-16 (3)
HFV-300

Dr. SETTEPANI. There was then a second memorandum, again from the supervisor, this time the Director of the Division of Toxicology, Dr. Farber, that explained away those two findings. He said the hyperplasia was judged to be not preneoplastic, and that the increase in the adenocarcinomas and adenomas were not drug-related. But I wanted to see more explanation of those decisions, and

I especially wanted to see the Cancer Assessment Committee meet on it because Dr. Farber is not a pathologist and we have pathologists on the Cancer Assessment Committee.

For the second case, he mentioned historical data, and we usually like a biostatistician to see the historical data and evaluate that, and that would have been done by the Cancer Assessment Committee, but it was not sent to them for evaluation.

Mr. **Weiss**. So, you had a number of serious concerns about this review.

Dr. **Settepani**. Yes, sir.

Mr. **Weiss**. When was clorsulon approved, Dr. Crawford? What was the date it was approved. Was it January 29, 1985?

Dr. **Crawford**. Yes, January 29.

Mr. **Weiss**. Now, Dr. Settepani, why did you wait until almost 2 months after clorsulon was approved before writing that you could not concur with its approval?

Dr. **Settepani**. I had it in my office a month, but I received it on February 13, which was after the approval.

Mr. **Weiss**. Is it customary for you to review a new animal drug approval package after a drug is approved?

Dr. **Settepani**. No, sir.

Mr. **Weiss**. And your position requires that you sign off prior to approval. Isn't that correct?

Dr. **Settepani**. Yes, sir, it is.

Mr. **Weiss**. But in this instance, the approval package was not submitted to you until some 2 weeks after approval. Is that right?

Dr. **Settepani**. The approval letter had been signed and gone out to the company, yes, sir. I was basically reviewing the approval package that goes into the Federal Register Notice, but I generally also review the approval package before the approval letter is signed; yes, sir.

Mr. **Weiss**. And the concerns that you would have raised—would have been the same had you [illegible] approval package before rather than after January 29, 1985, [illegible] correct?

Dr. **Settepani**. Yes, sir, it is.

Mr. **Weiss**. Dr. Zeeman, when were you asked to do a finding of no significant impact, or FONSI, for clorsulon?

Dr. **Zeeman**. That decision was made, I believe, about the time of January 23 when options were discussed in a meeting with Dr. Norcross and Mr. Matheson. And at that time we laid out some of the options, and it appeared that a preparation of a long FONSI that explained our concerns and laid out before the public what we knew about this drug was the most appropriate way to handle this.

Mr. **Weiss**. You were asked to do that somewhere around January 23?

Dr. **Zeeman**. Let's see. I think the decision whether to go with various options was made at that time, yes, and this was the option that was decided upon.

Mr. **Weiss**. How long were you originally given to do the finding of no significant impact?

Dr. **Zeeman**. Between 1 and 2 weeks.

Mr. **Weiss**. And how long did it take you?

Dr. **Zeeman**. About 2 weeks.

Mr. WEISS. And while you were working on the FONSI, the drug was approved. Is that right?

Dr. ZEEMAN. That is correct.

Mr. WEISS. Do not agency regulations require that an environmental finding of no significant impact be completed prior to the approval of a new animal drug?

Dr. ZEEMAN. I am not sure about that. I would have to ask Mr. Matheson. Yes, yes, that is correct.

Mr. WEISS. FDA regulations require the regulated industry to prepare and submit an environmental impact analysis report, or EIAR. A week before clorsulon was approved, your notes state that Merck's environmental impact analysis report for clorsulon was "[i]nadequate." One alternative you discussed in your notes was to use the "FONSI [to] fix [the] problems of [the] EIAR." Is this the alternative you chose?

Dr. ZEEMAN. Yes, it is.

[The notes referred to follow:]

Closulon

Major [illegible] Issues

A. Studies

1. Biodegradation Study → appears inadequate
2. Phytotox. – Prelim. Study Results → clearly indicate definitive test needed!
   – Labeling (or package insert)
3. Tests = Require post-approval testing (?!)

B. EIR ?

1. Inadequate : alternatives?

Longest time → a) Write long incomplete letter

[illegible] → b) Meeting to describe flaws [illegible] in EIR — wait for return & hope it's O.K.

Get what [illegible] in comment → c) Prepare FONSI (w/ [illegible]) that fixes problems of EIAR & outlines [illegible]

i) Problem = occasionally include info from studies & reports not in EIR

∴ Let Merck [illegible] agree to?

Sandy loam Soil
MK-[illegible] ([illegible])
0.19% CO2 [illegible]
0.05 [illegible]
Glean
29.62% CO2
2.21% volatiles

Silty loam
MK-[illegible]
0.20% CO2
0.09% volatiles
Glean
13.36% CO2
2.19% volatiles

Clay loam
MK-[illegible]
0.15% CO2
0.01% volatiles
Glean
17.28% CO2
2.13% volatiles

[illegible]
47 day Back & Flux [illegible] (8)
MK
0.01%
Glean
8.87%

MK
0.02%
Glean
7.38%

MK
5.40% [illegible]
Glean
0.57% [illegible]

Glean
All soils
(7, 1, 8) ⇒ 38.17%

17.95%

20.13%

Mr. **Weiss**. And was not correcting inadequacies in the EIAR the responsibility of the industry sponsor?

Dr. **Zeeman**. Usually.

Mr. **Weiss**. But you ended up doing it.

Dr. **Zeeman**. Yes.

Mr. **Weiss**. Why was that?

Dr. **Zeeman**. Basically because that would be the most accurate way to put the information before the public as quickly as possible.

Mr. **Weiss**. You expect sponsors to do accurate work, too, don't you?

Dr. **Zeeman**. I have that expectation; it has not often been reached.

Mr. **Weiss**. But do you often substitute your work for that of the sponsor in the preparation of the EIAR? What percent of the time do you do the sponsor's work of preparing an EIAR?

Dr. **Zeeman**. If what you are asking is do I evaluate their information and determine whether it is adequate or not, that is routine.

Mr. **Weiss**. Right.

Dr. **Zeeman**. Normally a FONSI is a fairly brief document that says that what has been submitted by the sponsor is adequate. And in that document we occasionally do make corrections when there is a difference in interpretation of data.

Mr. **Weiss**. What I would like to know is how routinely you use the FONSI to make such corrections?

Dr. **Zeeman**. Oh, I would say it is probably less than 10 percent of the time.

Mr. **Weiss**. Less than 10 percent, OK.

Dr. Zeeman, is it correct that clorsulon has been shown to be significantly toxic to plantlife at every level that it has been tested?

Dr. **Zeeman**. Some plants; five of eight plant species in a preliminary test gave indications that it caused plant stunting.

Mr. **Weiss**. CVM's January 23, 1985, statistical review states: "[A] no-effect level of clorsulon cannot be established from these studies." Is that for studies of eight crop plants, or for just five of the eight?

Dr. **Zeeman**. Five of the eight.

[The review referred to follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Memorandum

Date January 23, 1985

From Biometrics Branch, HFV-124

Subject STatistical Review of Phytotoxicity Study for Clorsulon

To Division of Drug and Environmental Toxicology
Environmental Staff, HFV-152
ATTN: Dr. Maurice Zeeman

NADA 136742C017
Clorsulon
Merck Sharp and Dohme
Rahway, New Jersey

As you requested, we have reviewed the "Statistical Analysis of the Clorsulon Phytotoxicity Study" submitted by the sponsor under cover letter dated January 10, 1984. We have no major criticisms with respect to these analyses. The firm's statisticians ran one-sided trend tests to determine if there were statistically significant negative dose-response trends in shoot weight for each of the test species. The results of these tests indicated that there were significant negative trends for all species. They then attempted to determine the minimum dose level for each species that produced significantly smaller shoot weights than the control (zero level) by using the trend test in a stepwise manner, sequentially dropping out higher dose levels as one proceeds toward zero.

This latter stepwise procedure suffers from the shortcoming that the detection power of the trend test steadily declines as we approach zero. At the lowest dose level tested the trend test is really a simple t-test comparison with the power of this comparison depending entirely on the number of replicates (pots) sampled. In the present case this was only 4 pots/group which is relatively small for toxicity testing. Nevertheless, the sponsor's statisticians found that even the lowest level of clorsuon tested (1 mg/kg) gave a detectable phytotoxic effect for 5 of the 8 plant species investigated. Consequently, a "no effect" level of clorsulon cannot be established from these studies.

With respect to the arguments raised regarding the validity of estimating a safe exposure concentration, for a plant species, by taking 1/100 of the lower 95% confidence limit of the EC_{50} for that species, we agree with the sponsor's statistician that, at least in the present situation, this procedure produces unreliable results. The 2.9 mg/kg safe "estimate" obtained here for oats is inconsistent with the more reliable, direct observation that there was a statistically significant reduction in shoot weights even at the 1 mg/kg dose level.

Summary

The statistical analysis of the phytotoxicity study is acceptable as presented. The results of the analysis indicate that at least some degree of phytotoxicity (i.e. reduction in shoot weight) was detectable even at the lowest dose level (1 mg/kg) of clorsulon tested.

If you have any questions regarding these comments, please let me know.

James J Colaianne

James J. Colaianne, Ph.D.
Mathematical Statistician
New Animal Drug Evaluation

Mr. Weiss. Five of the eight. Does this mean that FDA approved clorsulon, but did not know whether even lower levels than those tested would similarly damage plantlife?

Dr. Zeeman. The word severely is problematic for me.

Mr. Weiss. "Similarly, similarly" damage.

Dr. Zeeman. That was a possibility, and that was one of the reasons for putting the labeling on the product to indicate to the public that that might be a problem. And then we also had a commitment from the sponsor to do a definitive test of the phytotoxicity to determine whether or not this was an adequate preliminary study to increase the number of species to be tested and also the types of phytotoxic tests.

Mr. Weiss. Would you put into lay language what we are talking about?

Dr. Zeeman. Basically, the company would do—in this case, the company did a screening test. They tested various levels of clorsulon in the soil, and tested to see whether or not the plants grew as quickly and weighed as much after a 14-day period. And in five of the eight cases, at the lowest dose that was tested, they found some decrease in the plant weight in comparison to a normal population.

Mr. Weiss. So that it is the residues in the excretion of the animal receiving this drug that would have that kind of impact. Is that right?

Dr. Zeeman. Yes.

Mr. Weiss. Dr. Settepani, did this play a major part in your March 20, 1985, nonconcurrence memorandum?

Dr. Settepani. Yes, sir; it was one of the items. I usually tend to get more concerned about human food safety issues, but this was one of them.

Mr. Weiss. In fact, you noted that the lowest clorsulon level tested "approximates the concentration of the drug in urine and feces of treated cattle. What will we do if even lower levels of drug are found to exhibit phytotoxicity [that is, damage to plant life] now that the drug is approved."

[Dr. Settepani's March 20, 1985, memorandum is in the record.]

Mr. Weiss. You wrote this; isn't that correct?

Dr. Settepani. Yes, sir; and, as I mentioned, we found the other variable there, the actual level in the excreta was higher than I wrote at the time.

Mr. Weiss. Dr. Settepani, at the time that it approved clorsulon, did FDA have data on whether, and to what extent, the drug can damage pastures and crops exposed to residues of the drug in the feces and the urine of cattle?

Dr. Settepani. I really am not the best person here to answer that question.

Mr. Weiss. Dr. Zeeman.

Dr. Zeeman. Would you please repeat that?

Mr. Weiss. Yes; at the time that it approved clorsulon, did FDA have data on whether, and to what extent, the drug can damage pastures and crops exposed to its residues in the feces and urine of cattle?

Dr. Zeeman. You are saying on January 29?

Mr. Weiss. That is right.

Dr. **Zeeman**. OK. To my knowledge, there was an indication that there was a problem with some plants, most of them crop plants. The testing had not been done in relation to pasture grasses. That was one of the discussions we had with the firm, and additional plant species that Mr. Matheson discussed with the firm in terms of the pasture grasses that should be tested.

Mr. **Weiss**. Mr. Matheson, did FDA know whether clorsulon's toxic effects on plantlife are irreversible?

Mr. **Matheson**. We had an indication from the photodegradation data that had been submitted by the firm that the effects were probably reversible, especially in light of the two to three time a year dosing pattern for this product.

Mr. **Weiss**. And when did you receive that information?

Mr. **Matheson**. We had the photodegradation data as early as October? September or October 1984.

Mr. **Weiss**. Probably reversible, right?

Mr. **Matheson**. Probably reversible, yes, sir.

Mr. **Weiss**. Does FDA, now 6 months after clorsulon's approval, have definitive data defining the nature and extent of clorsulon's toxicity to pasture and crops, including data on no-effect levels and whether its toxic effects are reversible?

Mr. **Matheson**. No, sir, we do not.

Mr. **Weiss**. What efforts are being made to obtain that information?

Mr. **Matheson**. We have been in contact with the sponsor repeatedly since the approval. There were two groups of studies required as a commitment for approval of the product.

First was a biodegradation study to find out how persistent the material may be in the environment. We understand that that study has been completed, but the report has not been submitted to FDA yet.

But the phytotoxicity studies that you refer to, the protocols, we understand, are in preparation, but they have not been submitted to the agency for review at this time. We expect them any day now.

Mr. **Weiss**. Now, did not the Center's approval letter stipulate that those studies would be completed within 6 months?

Mr. **Matheson**. We have not seen a copy of the approval letter.

Mr. **Weiss**. Dr. Crawford, the second paragraph of the January 29 approval letter states: "[I]t is our understanding that you are firmly committed to conduct within the next 6 months the following environmental studies: 1. Biodegradation in Soils (definitive test); 2. Phytotoxicity: Seed Germination and Seedling Growth (definitive tests)."

[The January 29, 1985, approval letter follows:]

JAN 29 [illegible]

NADA 136-742

Kenneth G. Davis, D.V.M.
Director, Regulatory Affairs
Merck Sharp & Dohme Research Laboratories
P.O. Box 2000
Rahway, New Jersey 07065

Dear Dr. Davis:

Reference is made to your new animal drug application dated December 10, 1983, and all amendments including the January 10, 1985 submission. The latest submission is the revised EIA for CURATREM (clorsulon).

We have reviewed the application as amended and in accordance with your meeting with our staff, January 28, 1985, it is our understanding that you are firmly committed to conduct within the next six months the following environmental studies:

1. Biodegradation in Soils (definitive test)
2. Phytotoxicity: Seed Germination and Seedling Growth (definitive tests)

It is further understood that the following environmental warning statement will be highlighted at the next printing of labeling.

> Caution: Preliminary tests of eight crop plants (oats, corn, tomatoes, turnips, peas, beans, lettuce, and sunflowers) suggest that manure and urine from treated animals may contain enough clorsulon to cause stunting in pasture and crop plants. Definitive studies on clorsulon plant toxicity and degradation in soil are being conducted.

Your application is approved. A notice of this approval is being forwarded for publication in the FEDERAL REGISTER. In accordance with the Center's policy, this approval is effective immediately. You may initiate distribution and marketing of the product upon receipt of this letter.

Sincerely yours,

Lester M. Crawford, DVM, PhD
Director, Center for
Veterinary Medicine

cc: Orig, Dup, HFV-16
HFV-1
HFV-152
HFV-135
AGabuten/hmt 1/29/85

[illegible] 1/29/85

[illegible] 1/29/85

APP

Mr. **Weiss**. So, it was stipulated that those studies would be completed within 6 months. Is that correct?

Dr. **Crawford**. Yes.

Mr. **Weiss**. Mr. Matheson, does FDA know with certainty that an environmental impact statement will not need to be done once clorsulon's toxicity to plantlife is better defined?

Mr. **Matheson**. No, sir; we do not know with certainty. If I may expand on that?

Mr. **Weiss**. Please.

Mr. **Matheson**. There is a certain amount of unpredictability in any prediction we make about the environmental impacts of a product going into the environment. We are using laboratory data to predict something to occur in a very complex ecosystem, and there are interrelationships in an ecosystem that we cannot duplicate in the laboratory. So, there are always unexpected things that may come up.

In this case, it is more uncertain than we would like because we do not have all the laboratory data that we wanted for the time of the approval.

Mr. **Weiss**. According to section 25.1 of FDA's regulations, is not an environmental impact statement, if one must be undertaken, required to be done before a new animal drug is approved?

Mr. **Matheson**. Yes, sir; if we determine that a significant environmental impact would be expected, then an environmental impact statement should be prepared before the approval.

Mr. **Weiss**. I understand that the sponsor is required to conduct post-approval studies to determine whether clorsulon residues can damage pasture and crop plants, and is also conducting biodegradation studies to determine whether the drug persists for long periods in the environment. Dr. Zeeman, is it not normal procedure for such studies to be performed pre-approval rather than post-approval?

Dr. **Zeeman**. Yes, it is, Mr. Chairman.

Mr. **Weiss**. Would you have preferred to await the results of such studies before concurring in the drug's approval?

Dr. **Zeeman**. Most certainly.

Mr. **Weiss**. On September 12, 1984, 4 months before clorsulon was approved, Dr. Guest, you advised Merck that if the company had not completed a required biodegradation study by approval time, that FDA would "go ahead based on a commitment to complete the work after approval."

[Dr. Guest's memorandum of his September 12, 1984, meeting with a Merck representative is in the record.]

Mr. **Weiss**. Dr. Guest, you did advise Merck to that effect, did you not?

Dr. **Guest**. I did say that, Mr. Chairman, but you did omit one phrase that is a part of that memorandum.

Mr. **Weiss**. Which was?

Dr. **Guest**. My memorandum, my telephone memorandum of September 12, 1984, with Dr. Ken Davis said that—I indicated to Dr. Davis that if the study had not reached an end point by the time all other aspects are finished, and if there are no overriding circumstances, I told him at that time if there were no other problems that I could perceive that would cause this to be a problem, that we could go ahead based on a commitment.

Mr. **Weiss**. Dr. Zeeman, did FDA's environmental staff realize last September that clorsulon could be extremely toxic to plantlife?

Dr. **Zeeman**. No, we did not.

Mr. **Weiss**. CVM's statistician, in fact, did not complete his review of the clorsulon plant toxicity study until January 23, 1985, less than 1 week before clorsulon was approved. Isn't that correct?

Dr. **Zeeman**. The original environmental impact analysis report that we had received from the firm described in some detail the results of the phytotoxicity test. At that time, the firm had not submitted the study for review, and subsequently, in meetings and in writing, requested that they send us that study for review. And we received that study, let me see, October 30, 1984. That is when our review was. Mr. Matheson did the initial review on the phytotoxicity study information that was received. And I think it was inadequate, and we went back to the firm again to say do some statistics on this. And then that information was received and given to the statistical staff and their review resulted in that memorandum.

Mr. **Weiss**. And the statistician's review was completed less than 1 week before the drug's approval. Isn't that correct?

Dr. **Zeeman**. Yes.

Mr. **Weiss**. FDA did determine that its environmental concerns regarding clorsulon warranted a special warning on the drug's label. Dr. Zeeman, I understand that you met with a Merck representative on January 28, 1985, the day before clorsulon was approved, and emphasized the need for such a warning. What was his response?

Dr. **Zeeman**. He wanted to know if it was really necessary. To which Mr. Matheson and I said yes.

Mr. **Weiss**. In your January 29, 1985, approval letter, Dr. Crawford, you state that the clorsulon labeling should highlight an environmental warning statement which states: "Caution: Preliminary tests of eight crop plants * * * suggest that manure and urine from treated animals may contain enough clorsulon to cause stunting in pasture and crop plants."

[The January 29, 1985, approval letter is in the record.]

Mr. **Weiss**. I presume, then, that you believed that such a warning is necessary and appropriate?

Dr. **Crawford**. Yes.

Mr. **Weiss**. And, in fact, did not the finding of no significant impact [FONSI] for clorsulon state that the requirement of a warning label would "mitigate" any harm the drug would inflict on pastures and crops?

Dr. **Crawford**. Yes.

Mr. **Weiss**. Why then did you advise Merck in your January 29, 1985, approval letter that it could wait for the "next" printing of its labeling to include such a warning?

Dr. **Crawford**. I believe that the final printed labeling, Mr. Chairman, which is what we call FPL, had already been approved by the appropriate officials in the Center. And, therefore, I believe the product was already labeled, et cetera, and I determined that it probably would be sufficient, it would be sufficient to have a new labeling with the next printing, which we had been informed would be fairly soon.

Mr. **Weiss**. What other officials would have been in a position to approve labeling that did not include the warning that Dr. Zeeman stated was needed the day before clorsulon was approved?

Dr. **Crawford**. Well, the final printed labeling is approved by people in surveillance and compliance. They have to monitor the product once it is on the market. So, in fact, they take into consideration the views of Dr. Zeeman and others, and wind up agreeing with the firm or disagreeing with the firm, and finally approving how the product will be labeled. That is the last thing that is done in the drug approval process is the agreement as to how it can be labeled, and it is done by a different group than Dr. Zeeman.

Mr. **Weiss**. You mean Dr. Zeeman has no input?

Dr. **Crawford**. Yes, yes, he has input.

Mr. **Weiss**. Dr. Zeeman, when, prior to January 28, 1985, did you discuss with surveillance and compliance personnel what the labeling would state?

Dr. **Zeeman**. I do not remember having any conversation with surveillance and compliance people about the label.

Mr. **Weiss**. Can you describe what your role is in the labeling review process?

Dr. **Zeeman**. In a few circumstances when there were expected environmental consequences, we have requested that there be labeling on a product. For example, if materials will be toxic to fish and we expect that it is possible that it could get into water, then we think it is appropriate that warning label be put on the material.

I can make that recommendation and put it in my review. And what happens to it then is not always clear to me.

Mr. **Weiss**. But does the surveillance and compliance unit make final labeling decisions before receiving your recommendations?

Dr. **Zeeman**. I do not know.

Mr. **Weiss**. Well, as a general practice, does surveillance and compliance decide what the label should contain concerning matters within your purview before checking with you?

Dr. **Zeeman**. That does not, in my memory, appear to be a routine kind of approach, partly because we do not often have things to put on the label.

Mr. **Weiss**. Dr. Crawford, you spelled out in your January 29 approval letter what the environmental warning statement should say, right?

Dr. **Crawford**. Yes.

Mr. **Weiss**. So, what was the big deal about having the company reprint its labels?

Dr. **Crawford**. I do not know that—I do not recall exactly what those considerations were. The letter of approval was presented to me, and when I reviewed it, I remember going over each aspect of it. And I can only assume from my memory, Mr. Chairman, that I had been told that the product had already been labeled and prepared for distribution, and we wanted to put in the letter that it had to be changed as soon as possible, and this was the position we developed.

Mr. Weiss. What did you anticipate was meant by as soon as possible?

Dr. Crawford. With the next printing of the labeling.

Mr. Weiss. When did you expect that next printing to take place?

Dr. Crawford. I do not remember what the expectations were. Usually it is in a very short amount of time, though.

Mr. Weiss. Has the next printing taken place yet, to your knowledge?

Dr. Crawford. Yes, it is now on the label, the warning.

Mr. Weiss. When did it go on the label?

Dr. Crawford. Mr. Matheson informs me that the firm has informed him that it is on the label. We are not sure when it was distributed. So, it would not have happened before now; that is, within the last very immediate few days if, in fact, all of the product that is out there on the market is now labeled that way. So, it has been this length of time before it got on the label.

Mr. Weiss. So, 6 months after the fact, to the best of your knowledge, the warnings that you had said on January 29 were necessary, have still not been added to the label, or if they have been added, only within the last day or two.

Dr. Crawford. It is our impression they would have been very recently. What I would like to request of you, Mr. Chairman, is that we get a certification from the firm when it was placed and submit that for the record. It could have been earlier than this. We just cannot attest to the exact date at this point. I am sorry for that.

[The information requested follows:]

MERCK SHARP & DOHME RESEARCH LABORATORIES
DIVISION OF MERCK & CO., INC.
P.O. BOX 2000, RAHWAY, NEW JERSEY 07065-0914

R. R. BUCK
ASSISTANT DIRECTOR
REGULATORY AFFAIRS

(201) 750-8857

August 14, 1985

Dr. Andrew J. Beaulieu, Director
Division of Surveillance (HFV-210)
Center for Veterinary Medicine
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Beaulieu:

We are writing in response to a telephone call from Dr. Mason today regarding the labeling for our product CURATREM (Clorsulon) 8.5% Liver Fluke Drench for Cattle, NADA 136-742.

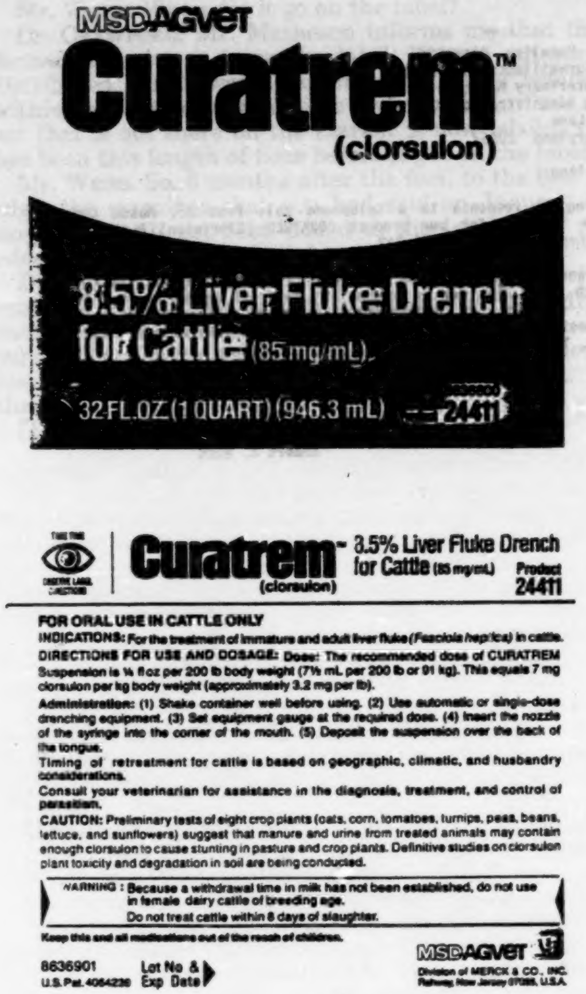
As per his request, attached are three copies of our current label for CURATREM which went into use on production material on April 24, 1985. These labels contain the environmental warning statement that Dr. Crawford requested be added at the next printing of labels in his letter of January 29, 1985 (copy attached).

Very truly yours,

Robert R Buck
Robert R. Buck

RRB:rfg
Attachment

MERCK & CO., Inc.
Rahway, New Jersey
AUG 14 1985



MSDAGVET
Curatrem™
(clorsulon)

8.5% Liver Fluke Drench for Cattle (85 mg/mL)

32 FL.OZ.(1 QUART) (946.3 mL)

Product 24411

TAKE TIME
OBSERVE LABEL DIRECTIONS

Curatrem™
(clorsulon)
8.5% Liver Fluke Drench for Cattle (85 mg/mL)
Product
24411

FOR ORAL USE IN CATTLE ONLY

INDICATIONS: For the treatment of immature and adult liver fluke (*Fasciola hepatica*) in cattle.

DIRECTIONS FOR USE AND DOSAGE: Dose: The recommended dose of CURATREM Suspension is ¼ fl oz per 200 lb body weight (7½ mL per 200 lb or 91 kg). This equals 7 mg clorsulon per kg body weight (approximately 3.2 mg per lb).

Administration: (1) Shake container well before using. (2) Use automatic or single-dose drenching equipment. (3) Set equipment gauge at the required dose. (4) Insert the nozzle of the syringe into the corner of the mouth. (5) Deposit the suspension over the back of the tongue.

Timing of retreatment for cattle is based on geographic, climatic, and husbandry considerations.

Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasitism.

CAUTION: Preliminary tests of eight crop plants (oats, corn, tomatoes, turnips, peas, beans, lettuce, and sunflowers) suggest that manure and urine from treated animals may contain enough clorsulon to cause stunting in pasture and crop plants. Definitive studies on clorsulon plant toxicity and degradation in soil are being conducted.

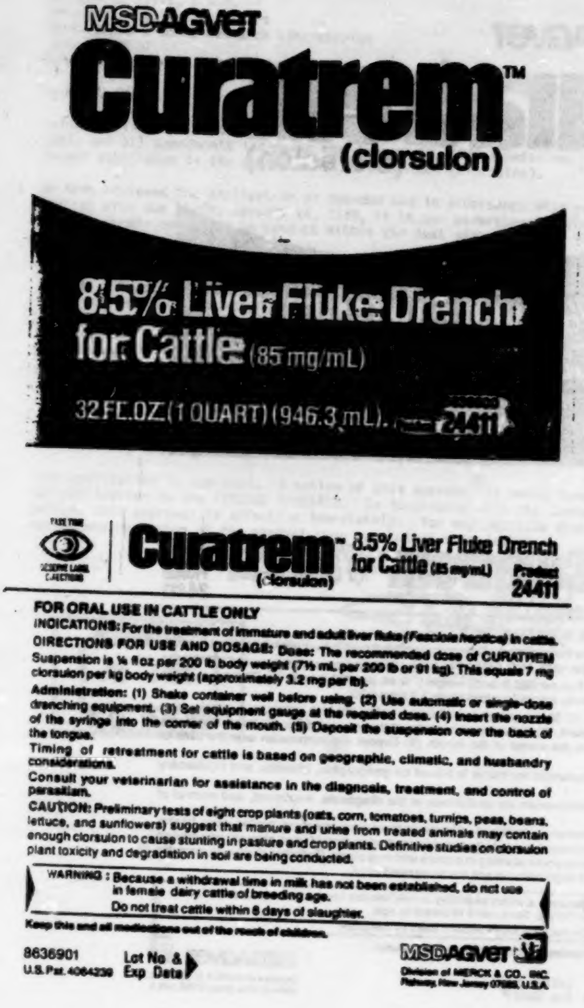
WARNING: Because a withdrawal time in milk has not been established, do not use in female dairy cattle of breeding age.
Do not treat cattle within 8 days of slaughter.

Keep this and all medications out of the reach of children.

8636901
U.S. Pat. 4064236
Lot No &
Exp Date

MSDAGVET
Division of MERCK & CO., INC.
Rahway, New Jersey 07065, U.S.A.

MERCK & CO., Inc.
Rahway, New Jersey
[illegible] 14 1985



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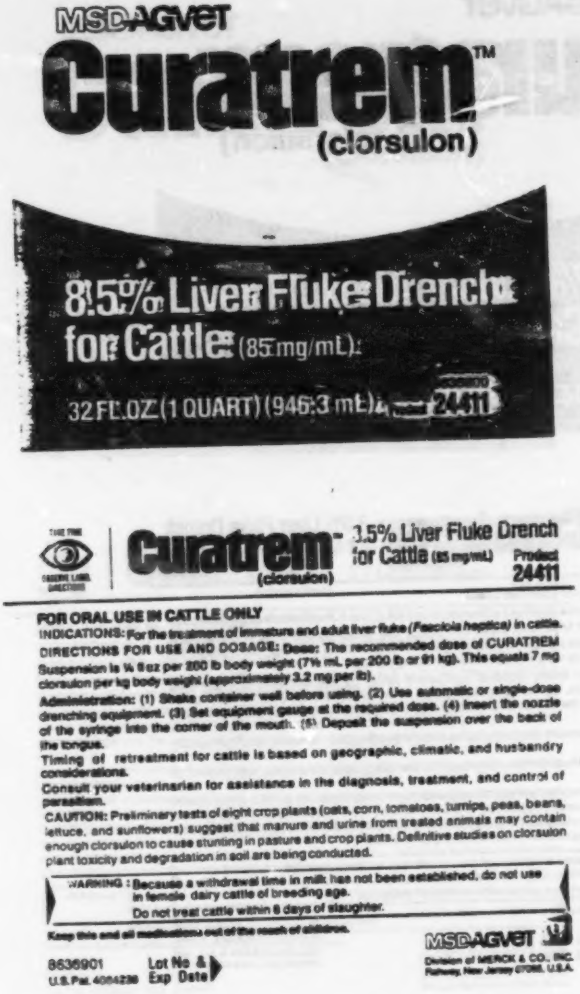
MERCK & CO., Inc.
Rahway, New Jersey
AUG 14 1985



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U.S. Pat. 4064239

Lot No. &
Exp Date

MSDAGVET
Division of MERCK & CO., INC.
Rahway, New Jersey 07065, U.S.A.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JAN 29 1985

NADA 136-742

Kenneth G. Davis, D.V.M.
Director, Regulatory Affairs
Merck Sharp & Dohme Research Laboratories
P.O. Box 2000
Rahway, New Jersey 07065

Dear Dr. Davis:

Reference is made to your new animal drug application dated December 10, 1983, and all amendments including the January 10, 1985 submission. The latest submission is the revised EIAR for CURATREM (clorsulon).

We have reviewed the application as amended and in accordance with your meeting with our staff, January 28, 1985, it is our understanding that you are firmly committed to conduct within the next six months the following environmental studies:

1. Biodegradation in Soils (definitive test)
2. Phytotoxicity: Seed Germination and Seedling Growth (definitive tests)

It is further understood that the following environmental warning statement will be highlighted at the next printing of labeling.

> Caution: Preliminary tests of eight crop plants (oats, corn, tomatoes, turnips, peas, beans, lettuce, and sunflowers) suggest that manure and urine from treated animals may contain enough clorsulon to cause stunting in pasture and crop plants. Definitive studies on clorsulon plant toxicity and degradation in soil are being conducted.

Your application is approved. A notice of this approval is being forwarded for publication in the FEDERAL REGISTER. In accordance with the Center's policy, this approval is effective immediately. You may initiate distribution and marketing of the product upon receipt of this letter.

Sincerely yours,

Lester M Crawford

Lester M. Crawford, DVM, PhD
Director, Center for
Veterinary Medicine

RECEIVED
FEB 1 1985
K.G. DAVIS

Mr. **Weiss**. Well, who had responsibility for following up to inquire whether the required warning statement was being placed on the label?

Dr. **Crawford**. It is the Center of Veterinary Medicine's responsibility. It is my ultimate responsibility.

Mr. **Weiss**. But you do not know as of this moment when it was placed on the label or, for that matter, whether it has been added to the label.

Dr. **Crawford**. We know that it has been placed on, but we cannot give you the exact date.

Mr. **Weiss**. Do you know whether new labels have been printed or whether a warning sticker has been placed on the original labels?

Dr. **Crawford**. It is——

Mr. **Weiss**. Or what size the warning is?

Dr. **Crawford**. It is a reprinting of the label.

Mr. **Weiss**. I assume that you agree that farmers and the livestock industry should have this information so that they can determine whether or in what manner they want to use the drug.

Dr. **Crawford**. Yes, we believe that the livestock producers should have the advantage of having that on the label.

Mr. **Weiss**. The bells have rung. We will break in just a few moments for the vote. And then we'll return.

But, before we do, I want to return to the discussion we had at the very opening of today's session regarding matters which FDA considers confidential. The agencies of the Government whom we have the responsibility to oversee constantly make blanket requests for nondisclosure of all material they supply us. I want to place in the record, at this time, a June 5, 1984, letter from the subcommittee responding to such a request from FDA. It is addressed to Robert C. Wetherell, Jr., Associate Commissioner for Legislation and Information, FDA's Office of Legislation and Information. The letter states:

> Your letter of June 4 to the Newark Beth Israel Center, a copy of which was delivered to the subcommittee today, requires clarification.
>
> Should the FDA wish to limit circulation of documents provided to the subcommittee, your office should specifically identify each document it considers confidential and FDA's basis for requesting nondisclosure when the documents are made available to the subcommittee. It is not reasonable to expect the Chairman to consult with you before decisions are made to include agency documents in subcommittee hearing records. He will, of course, make every attempt to accommodate legitimate requests for nondisclosure.

That letter was signed by our staff director, Mr. Gottlieb, and that, indeed, has been the position of the subcommittee throughout my chairmanship.

I'm going to ask unanimous consent to have that letter entered into the record.

[The letter referred to follows:]

NINETY-EIGHTH CONGRESS

Congress of the United States
House of Representatives
INTERGOVERNMENTAL RELATIONS AND
HUMAN RESOURCES SUBCOMMITTEE
OF THE
COMMITTEE ON GOVERNMENT OPERATIONS
RAYBURN HOUSE OFFICE BUILDING, ROOM B-372
WASHINGTON, D.C. 20515
[illegible]

E-Israel

June 5, 1984

Robert C. Wetherell, Jr.
Associate Commissioner for
  Legislation and Information
Office of Legislation and Information
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear ~~Mr. Wetherell:~~ Bob

Your letter of June 4 to the Newark Beth Israel Medical Center, a copy of which was delivered to the subcommittee today, requires clarification.

Should FDA wish to limit circulation of documents provided to the subcommittee, your office should specifically identify each document it considers confidential and FDA's basis for requesting nondisclosure when the documents are made available to the subcommittee. It is not reasonable to expect the Chairman to consult with you before decisions are made to include agency documents in subcommittee hearing records. He will, of course, make every attempt to accommodate legitimate requests for nondisclosure.

The Chairman would appreciate your immediately supplying him a copy of the May 14, 1984, letter from Newark Beth Israel Medical Center.

Sincerely,

James R. Gottlieb
Staff Director

Mr. Weiss. At this point, we'll take a break for about 10 or 15 minutes, and then we'll pick up.

The subcommittee stands in recess.

[Recess taken.]

Mr. Weiss. The subcommittee is back in session.

Let's return to FDA's regulation of albendazole. When, Dr. Crawford, did FDA first discover problems in controlling use of the drug?

Dr. Crawford. You mean distribution problems in the field?

Mr. Weiss. Yes.

Dr. Crawford. We began very early on being concerned about distribution patterns. If I may, I would like to ask Dr. Guest, if he wouldn't mind, to comment on when he thinks it first occurred, and then I'll follow up.

Mr. Weiss. Dr. Guest.

Dr. Guest. Mr. Chairman, I could not give you very precise dates, but it was the kind of program that we were watching fairly closely, and it was also the kind of program where if there were deviations from the distribution system, we had lots of people out there looking for it and telling us about it.

I think the key is that probably soon after 1979 or 1980, as these things came to our attention, we would correct them. And you correct those things in the way of either regulatory actions or warning letters, or a series of meetings and adjustments that had to do with the drug's sponsor. My recollection is that any time we ran across those things, we responded and corrected them just as quickly as we possibly could.

Mr. Weiss. As a matter of fact, an August 12, 1980, FDA memorandum indicates that agency inspectors had found serious problems in controlling the use of albendazole in Texas:

"There were no investigational records, no contact by Norden [the SmithKline subsidiary distributing the drug], no forms filled out, and no regard for the withdrawal period."

[The memorandum referred to follows:]

AUG 13 1980

MEMO OF TELECON
AUGUST 12, 1980

Frank Pugliese
Chief, Document Review Branch

Gary Pierce
DAL-DO

Mr. Pierce called regarding a just-completed inspection of Lubbock Feedyards, Lubbock TX, as a follow-up to a reported misuse of albendazole.

Mr. Pierce stated that it appeared that the Norden distribution center, the veterinarian and the feedlot managers all exhibited a lack of compliance with the conditions under which albendazole may be used. There were no investigational records, no contact by Norden, no forms filled out, and no regard for the withdrawal period. The EIR was being submitted to Compliance Branch.

I asked that a copy of the EIR be sent to us immediately, so that we could be ready for a prompt action when the completed report is in. He said he would do this.

Mr. Pierce then described an unrelated situation in which Norden apparently shipped 500 gallons of albendazole to a veterinary distributor. This is also in violation of the conditions of exemption. Mr. Pierce indicated that an inspection of the distributor should be made, but that the 3 inspections provided in the instruction memo had already been made. I said this would be a for-cause inspection, rather than a surveillance inspection, and the 3-inspection limit didn't apply. Mr. Pierce said he would proceed to set the inspection up. I offered to send an assignment memo if needed; Mr. Pierce said he'd call if one was necessary.

Frank G. Pugliese

cc:
HFV-1
HFV-9✓
HFV-200
HFV-230
HFV-234
HFR-6100
HFR-6150
HFR-7100
[illegible]

TO: Director, Investigations Branch
Dallas District Office

DATE: 8/5/80

FROM: Lubbock RIC

SUBJECT: Special Investigation - Albendazole Suspension INAD-2433 Cattle

RE: Norden Laboratories
Fort Worth, TX (Shpr)

Lubbock Feed Lots, Inc.
Lubbock, TX (DLR)

Deyhle Veterinary Services, Inc.
Drawer H
Clarendon, TX 79226
806-874-3533 (V[illegible].)

During the week of 7/29/80, an inspection was made at Lubbock Feed Lots, Inc., and samples were collected documenting the feed lot receiving Albendazole and using it to treat liver flukes in some 2793 head of cattle, and selling 11 head of cattle before the 180 withdrawal period. Three head had been sold to slaughter with 1 steer sold for slaughter 3 days after treatment with Albendazole.

This investigation was of Deyhle Veterinary Services, Inc., Clarendon, TX. A call was made to Dr. Deyhle and an employee answered. He reported that Dr. Deyhle would be at the firm in the morning and into the afternoon. With that information, I drove from Lubbock, TX to Clarendon, TX. I found Dr. Deyhle and spoke to him. At that time, he reported that his files for Lubbock Feed Lots were with his son who was making a call in Sweetwater, TX and then flying to Lubbock later in the day. Dr. Deyhle reported that he was flying to Lubbock and would fly me down and fly me back to Clarendon, TX. I replied that I would meet them in Lubbock, TX. I then drove back to Lubbock, TX.

At 4:18 PM, I issued a Notice of Inspection to Charles Deyhle and showed him and his son Charles Deyhle my credentials. I asked for Dr. Deyhle's file on the use of Albendazole and the treatment of cattle located at Lubbock Feed Lots. His file was a manila folder with a list of lot numbers, pen numbers, and number of head of cattle per pen. The lot numbers coincided with those received from Lubbock Feed Lots, Inc., however, the number of cattle were short.

Cattle Lot #	Lot Record Card # of Head	Dr. Deyhle # Head	Difference
699	366	364	-2
700	300	298	-2
701	288	283	-5
702	275	274	-1
707	200	200	0
708	200	200	0
709	249	248	-1
710	260	258	-2
711	320	318	-2
714	187	184	-3
715	148	146	-2
			-20

Dr. Deyhle reported that he got the head count from a computer printout and that he did not know the date of that printout. The printout would probably be at a later date and did not account for deaths and/or sales from the original entry on the lot record cards.

Dr. Deyhle provided me with a copy of a note from David Harbar, Norden, requesting that Dr. Deyhle sign the enclosed form (Albendazole Suspension Order Form) and a copy of the order form signed 2/15/80. It also requested the shipment of 32 gallons of Albendazole to be shipped to Lubbock Feed Lots, Lubbock, TX. Dr. Deyhle also provided me blank copies of both pre-treatment form and post-treatment form as sent to him by Norden Labs. As of 8/5/80, neither form had been filled out. Dr. Deyhle filled out a copy of the pre-treatment form at this time. I did not take a copy of the complete form because the animal owner/agent blank was not signed. Dr. Deyhle reported he would have Mr. Terry Crofoot sign the pre-treatment form and see that I got a copy.

The copy of Mr. David Harbor's note to Dr. Deyhle and a copy of order form dated 2/15/80 and a blank pre-treatment and post-treatment forms and Dr. Deyhle's affidavit were identified with DOC 80-265-336 and are to be attached with that C/R. Dr. Deyhle reported to me that he had done INAD work with Diamond Shamrock and was familiar with the research and record keeping program. He also informed me that the representative from Norden Laboratories did not inform him that he was in a research program. The pre-treatment form was not required by Norden before shipping the Albendazole nor has anyone from Norden made any follow-up requesting the pre-treatment form.

Dr. Deyhle reported only 1 firm, Lubbock Feed Lots, Inc., is using Albendazole under his supervision and the product was shipped directly to the feedlot. Dr. Deyhle is not keeping any inventory of the drug other than the record that 32 gallons were shipped to Lubbock Feed Lot, Inc.

I asked Dr. Deyle about the cattle coming from Navarro County, TX, a county not identified as a liver fluke area. He reported that Navarro County was only a stopping place for the cattle. He reported that the cattle originated on the Texas coast and he did not know that location.

I asked Dr. Deyhle if he had personal knowledge that the cattle had liver flukes. He reported that they were from a liver fluke area and someone may have posted some cattle. He did not know. It was reported to him that they did have flukes.

I asked Dr. Deyhle if he planned on filing the post-treatment report to include the number of livers condemned at slaughter due to liver fluke infection. He told me that as far as he knew or had been told that was not part of the program. He further stated that he had not been told to keep any records regarding morbidity, mortality, incidents or severity of liver flukes in the treated cattle. He reported that he had informed Terry Crofoot that cattle treated with the Albendazole must be held 180 days before being sold.

Ralph D Godfrey

Ralph D. Godfrey
Lubbock RIC

RDG/cab: 8/11/80

Mr. Weiss. Similar problems were identified around this time in Florida.

[An August 20, 1980, memorandum from FDA's Tampa Resident Post regarding insufficient controls over the distribution and use of albendazole follows:]

Memorandum

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Orlando District (HFR-4200)

DATE: August 20, 1980

FROM : Investigator
Tampa Resident Post (HFR-4585)

Vet: William C. Jeter, D.V.M.
205 West Clinton Avenue
Dade City, FL 33525

SUBJECT: Investigation Assignment
INAD 2433 - Cattle, Special
Liver Fluke Program

Distr: M & M Supply Company
of Florida Corporation
P. O. Box 248
Thonotosassa, FL 33592

This was a special investigation covering the receipt and dispensing of the INAD-2433 (cattle) Albendazole. This drug is considered an Investigational New Drug for the treatment of liver flukes. The Bureau of Veterinary Medicine Memo of February 1980, DHEW Pub. No (FDA) 80-6038, outlines the procedures to be used for the Special Liver Fluke Program.

Under the terms of this program, a veterinarian and producer have to sign forms agreeing to the conditions for the use of the drug. The drug Albendazole is manufactured by Norden A. Smith-Kline Company, Lincoln, Nebraska 68501. This drug was distributed in the Florida area by Norden Laboratories, Inc., Miami, Florida. Also stipulated in the BVM memo (page 4) is that the Albendazole may be obtained only through a veterinarian.

To: Bureau of Veterinary Medicine (HFV-234) September 12, 1980

Investigation of Dr. Jeter reveals he is not adequately fulfilling his obligations as an investigator in that he has delegated responsibility for contacting clients, explaining the program, and dispensing the drug to M&M Supply Company.

The investigator was able to reconcile the amount of drug dispensed with the amount received (180 gallons).

John J. Miceli
John J. Miceli
Supervisory Investigator

Attachments

cc: KAN-DO (HFR7150) w/attachments
TMP-RP (HFR-4585)

Buy U.S. Savings Bonds Regularly on the Payroll Savings Plan

An inspection of Norden Laboratories, Inc., Miami, Florida, on 6/20/80, shows that a Dr. W. C. Jeter, Town and County Veterinary Clinic, 405 East Clinton Avenue, Dade City, Florida, received 180 gallons of Albendazole.

On 8/14/80, credentials were shown and Notice of Inspection was issued to William C. Jeter, D.V.M., at the above listed address.

According to Dr. Jeter, he is overall responsible for the conduct of the Special Liver Fluke Program. Dr. Jeter was aware that Norden Labs was providing the Albendazole, and that he should be the individual dispensing it.

Dr. Jeter has delegated the responsibility of contacting the clients, explaining the program and dispensing the drug to the M & M Supply Company. Page 2 of the D.V.M. memo states the veterinarian is responsible. According to Dr. Jeter he has placed four orders with Norden (Miami), on 3/5/80 for 120 gallons, 3/27/80 for 100 gallons, 4/14/80 for 40 gallons and 8/12/80 for 16 gallons. Copies of Norden Albendazole Suspension Order Forms are attached. As of this date, Dr. Jeter has received 180 gallons of Albendazole, Invoice # 75926, 4/21/80, 40 gallons; Invoice # 65959, 4/7/80, 100 gallons; and Invoice #54945, 3/17/80 40 gallons. (The 100 gallon shipment was sent directly to M & M Supply Company).

Reviewing the Albendazole Suspension Pretreatment forms, it was observed that 191 gallons of Albendazole had been dispensed yet only 180 gallons had been received. Dr. Jeter could not explain this discrepancy, and I left for the M & M Supply Company.

Credentials were shown and Notice of Inspection was issued to Mr. Gerald D. Grosh, Manager of M & M Supply Company on 8/14/80. I requested copies of the firm's invoices showing the sale of Albendazole. According to the invoices, M & M had dispensed 166 gallons of Albendazole and 1/1 gallons of Albendazole had been broken in shipment. Copies of invoices covering the sale of Albendazole and M & M claim for the broken gallons are submitted as exhibits. Thirteen gallons of Albendazole had been sold to R. H. Chesser, Sebastian, Florida; however, there was no invoice covering this sale, because the salesman was on vacation. These figures account for 180 gallons of Albendazole.

Dr. Jeter does not have office hours on Thursday afternoons, and I returned to his office Friday and compared invoiced sales against the amount clients were to receive. The following discrepancies were noted:

Pretreatment Form: Client - James T. Mizell, Arcadia, Florida, on 4/10/80 was to receive 4 gallons. M & M invoice #1292 reflects one gallon being despensed on 4/24/80.

Client - Jack Kelly, Leigh Acres, Florida, on 4/7/80, was to receive 8 gallons. On 8/14/80, according to Mr. Grosh, there was no sale made to Mr. Kelly. Returning to M & M on 8/18, Cameron Burns, Assistant Manager, informed me that Mr. Kelly received his 8 gallons from the firm's Okeechobee plant and supplied me with Invoice #1397, 5/5/80 for 8 gallons of Albendazole. These 8 gallons are not used in determining the dispensing of the 180 gallons received.

Client - R. H. Chesser, Sebastian, Florida, was to receive 14 gallons, client's form dated 7/30/80. According to M & M, Mr. Chesser received 13 gallons, but they have no invoice covering the salesman because the salesman has not turned in his sales.

Dr. Jeter was under the impression that when the client signed the Pre-treatment form, the Albendazole was dispensed the same day.

On 8/18/80, I returned to M & M Supply Company and met with Mr. Cameron Burns, Assistant Manager. According to Mr. Burns, the Albendazole is not dispensed on the day the client signs the pretreatment form. This is simply setting up the program. When asked about Mr. Mizell receiving only one gallon of Albendazole when the client's form lists 4 gallons, Mr. Burns said that the cost of the drug probably made him change his mind. Albendazole is sold to the clients between $109 and $115.

On 8/19/80, I visisted the Hanock Ranch, Route #1, Box 387, Arcadia, Florida 33825 (telephone (813) 494-0188), and met with Mr. John R. Lawrence, General Manager. According to Mr. Lawrence, he has not used the Albandozole yet. Mr. Lawrence went on to say that he will begin to use it after he gets through examining the cattle which will be very shortly.

The following list gives the client's name, amount of Albendazole calculated to be used, date of visiting the client, M & M Invoice number, amount sold and date of sale. Exhibits attached correspond with the listed number of the client.

1. Deer Park Ranch - 3/27/80 - 500 Head of Cattle
   Star Route Box 1200
   Melbourne, Florida 8 gallons Albendazole
   Exhibit 1, M & M Invoice D50983, 4/10/80 for 8 gallons

2. Bently Braham Ranch, Inc. - 3/19/80 - 2,000 Head of Cattle
   P.O. Box 629
   Winter Haven, Florida 40 gallons Albendazole
   Exhibit 2, M & M Invoice D51129, 4/9/80 for 40 gallons.

3. Hancock Ranch - 3/26/80 - 2,5000 - 2,500 Head of Cattle
Route #1, Box 387
Arcadia, Florida 33825 - 80 gallons of Albendazole
Exhibit #3, Invoice D51151, 80 gallons 4/10/80

4. DeSota Correctional Institute - 4/10/80 - 322 Head of Cattle
Arcadia, Florida - 4 gallons Albendazole
Exhibit #4, M & M Invoice D51192, 4 gallons 4/17/80

5. James T. Mizell - 4/10/80 - 225 Head of Cattle - 4 gallons
P. O. Box 1334
Arcadia, Florida 33822
Exhibit 5, M & M Invoice E1292, 4/24/80 - 1 gallon
Exhbiit 5A, Pretreatment Form - listing 4 gallons

6. Lewis Hall, Jr. - 4/25/80 - 600 Head of Cattle
Tiger Bay Ranch
200 W.E. First Street
Miami, Florida 33131 - 10 gallons Albendazole
Exhibit #6, M & M Invoice E 1385, 5/1/80 for 10 gallons

7. Bronson, Inc. - 5/20/80 - 500 Head of Cattle - 8 gallons Albendazole
P.O. Box 879
Kissimmee, Florida 32741
Exhibit #7, M & M Invoice E2005, 5/27/80, 8 gallons of Albendazole

8. Margie Flint - 7/30/80 - 32 Head of Cattle - 1 gallon Albendazole
Route #2, Box 673
Acerdia, Florida
Exhibit #8, M & M Invoice E4244, 7/29/80 for 1 gallon

9. W. R. Flint - 6/6/80 - 128 Head of Cattle - 2 gallons Albendazole
155 Homestead Road
Leigh Acres, Florida - 2 gallons of Albendazole
Exhibit #9, M & M Invoice #1892, 6/2/80 2 gallons of Albendazole

10. H. L. Bowling - 7/11/80 - 600 Head of Cattle
239 East Tarpon
Port Charlotte, Florida - 12 gallons of Albendazole
Exhibit #10, M & M Invoice E3970, 7/11/80 12 gallons Albendazole

11. Jack Kelly - 4/7/80 - 400 Head of Cattle
P. O. Box 1017
Leigh Acres, Florida 33936 - 8 gallons of Albendazole
Exhibit #11, M & M Invoice E13976, 5/5/80 8 gallons. According to M & M the Albendazole was shipped from their Okeechobee, Florida office.

Exhibit 11A, Pretreatment Form listing 8 gallons.

12. R. H. Chesser - 7/30/80 - 700 Head of Cattle
Chesser Cap Road
Star Route 812
Sebastian, Florida - 14 gallons of Albendazole
According to M & M, they do not have the invoice covering this Sale. They also stated the Mr. Chesser received only 13 gallons not the 14 gallons as listed. The salesman is on vacation, and the invoice was not turned in.
Exhibit 12, Pretreatment Form listing 14 gallons.

Total of sales is 179 gallons, 1 gallon broken in shipment, resolves the 180 gallons of Albendazole received.
Other exhibits attached:

Exhibit 13, 14, 15, and 16 copies of the Albendazole Order Form.

Exhibit 17 M & M Presentation of Loss and Damage claim showing one gallon of Albendazole broken in shipment. The claim lists 26 cases as being received. According to M & M one case contained the Albendazole Suspension Treatment procedures.

On page 1 of the affidavit signed by M & M, the figure of 192 gallons dispensed should read 191 gallons. This was not noted until I returned to the office. No attempt was made to correct this error.

Ralph H. Chambers
Ralph H. Chambers

Mr. Weiss. Was any thought given in CVM during this period to terminating the emergency INAD program because of such problems, Dr. Crawford? Dr. Guest.

Dr. Crawford. Dr. Guest will follow up, if he likes. In every step along the way, Mr. Chairman, as Dr. Guest has mentioned, when these kinds of problems were uncovered by FDA field forces, we took what we considered appropriate steps. We met with the firm, and tried to get compliance, and generally, were satisfied with that.

We also, on one occasion, wrote one of the cooperating States, and threatened termination of the approval for that State. And always in the back of our mind was the fact that unless we could get compliance, we may have to terminate the INAD.

Mr. Weiss. And, in fact, didn't your then principal legal advisor, Mr. Fred Degnan, suggest that you reassess the wisdom of continuing the albendazole INAD program?

Dr. Crawford. Mr. Degnan joined all of us in being uncomfortable about the nature of the approval, and on a number of occasions, recommended that we either tighten up or that we consider the threat of suspension of the INAD.

Mr. Weiss. In an August 5, 1980, memorandum to Dr. Guest, Mr. Degnan wrote:

> I think the propriety of continuing the INAD has been called into question and perhaps it's time for us to reassemble our committee . . . to determine what action if any we should now take with regard to continuing to authorize the investigational use of albendazole.

[The memorandum referred to follows:]

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELF
OFFICE OF THE SECRETARY
Office of the General Counsel

TO : Dr. Gerald Guest (HFV-1) DATE: August 5, 1980

FHD

FROM : Fred H. Degnan (GCF-1)

SUBJECT: Albendazole

Both Joe Settepani and Dick Lehmann have advised me of what appear to be violations in the use of albendazole. Evidently feedlot cattle have been administered albendazole, and several railers from the feedlot have been shipped to market. This factual scenario raises several questions:

1. Are the conditions of use of albendazole as prescribed in the INAD being followed?

2. In light of the fact that some feedlot cattle have been administered albendazole, it is reasonable to assume that at the feedlot for which we have information all cattle have received albendazole. Therefore, shouldn't we monitor that feedlot not to mention consider seizing violative animals or carcasses and instituting a full inspection of the circumstances giving rise to the abusive use of albendazole?

In your new position, I'm not sure what involvement you can or want to take regarding albendazole. I think the propriety of continuing the INAD has been called into question and perhaps it's time for us to reassemble our committee, either with you or with your designee, to determine what action if any we should now take with regard to continuing to authorize the investigational use of albendazole.

cc: Dr. Settepani ✓
Dr. Lehmann
Mr. Geyer
Ms. April

Mr. **Weiss**. Dr. Guest, did you undertake in 1980 any reassessment of whether to continue the albendazole program?

Dr. **Guest**. I don't recall that specific recommendation, Mr. Chairman, but I think there was sensitivity within the agency and with me in particular, that I'm certain that we did what Mr. Degnan recommended at that time.

Mr. **Weiss**. Well, would you search your records and submit to us for the record whatever documentation or records you have of any reassessment efforts. Please describe what they entailed—for example, what kind of meetings were held, what kind of determinations or decisions were made regarding reassessment, etc., OK?

Dr. **Guest**. Yes, sir, I will.

[The information requested follows:]

The memorandum did not prompt any particular action. The field assignments which initiated monitoring albendazole use were issued in April 1980 by the Center and more specific assignments were issued throughout the period of albendazole usage. The Subcommittee has been provided copies of these field assignments.

Mr. **Weiss**. According to Mr. Gary Dykstra of CVM's Office of Surveillance and Compliance, by "1982, the Center began to see a breakdown" in "the system of monitoring and controlling albendazole's uses." As earlier noted, FDA told the sponsor in 1979 that the INAD program was to be immediately terminated if such uses were not stringently monitored and controlled. Did the Center take any action in 1982 to discontinue the use of albendazole?

Dr. **Crawford**. Mr. Chairman, may I ask the date of that memorandum, because Mr. Dykstra was not with the Center until late 1982, I believe?

Mr. **Weiss**. In the memorandum I quoted, which is dated August 13, 1984, he refers back to the history of the emergency INAD program and, at the top of page 4 of the memorandum, reportedly states: "In 1982, the Center began to see a breakdown in this system."

[The memorandum referred to follows:]

MEMORANDUM OF CONFERENCE

August 13, 1984
9:00 AM
Conference Room M

Between: FDA

Dr. M.A. Norcross,	HFV-100
Dr. R.A. Carnevale,	HFV-100
Dr. J. Colaianne,	HFV-124
Dr. C. Haines,	HFV-133
Mr. G. Dykstra,	HFV-200
Dr. J.A. Settepani,	HFV-301
Dr. R.L. Benson,	HFV-320
Dr. S.C. Fitzpatrick,	HFV-320
Dr. J.W. Hauswirth,	HFV-330
Dr. T.L. Farber,	HFV-330
Dr. N.E. Weber,	HFV-340

and

SmithKline Animal Health Products

Mrs. H.H. Birkhead
Mr. D. Hinnah
Dr. E. Lang
Dr. T. Wishousky
Dr. F.L. Carlborg
Dr. H. Theodorides
Dr. L. Free.

Subject: Emergency Use of Albendazole
INADs 2433, 2434

Dr. Norcross opened the meeting by saying that SE/HFS had concluded that albendazole caused an oncogenic response in the chronic feeding studies in rodents. Presently there was no method validated at an appropriate level to monitor albendazole under the emergency INADs to insure that the 180-day withdrawal time was being complied with. Finally, the Division of Compliance had some evidence of misuse of albendazole under the emergency INADs. The purpose of this meeting, requested by the agency, was not to discuss the scientific issues involved but to discuss the status of the emergency INADs which allow commercial marketing of albendazole. Dr. Norcross handed out an agenda for the meeting (Attachment I) and asked if the sponsor had received all the relevant CVM documents on this issue.

Mrs. Birkhead replied that she had received the memorandum from Dr. Settepani, the memorandum of the Cancer Assessment Committee dated July 26, 1984, and the statistical memoranda dated July 17, 1984, August 1, 1984 and August 8, 1984.

Mrs. Birkhead ~~stated~~ that it was also the sponsor's desire to separate the question of oncogencity of albendazole from the questions regarding the status of the emergency INADs. The sponsor has not had enough time to review throughly the decision of the Cancer Assessment Committee. The sponsor was prepared to address the issue of the emergency INADs.

Dr. Farber briefly discussed the toxicology. He stated that he felt the CAC memorandum was clear as to the discussions and conclusions regarding albendazole and therefore he would not go over it again. Instead he asked the sponsor if they had any questions.

Dr. Theodorides began by reiterating that they needed more time to evaluate our conclusions and would like Dr. Furrow present to discuss the pathology. Mrs. Birkhead added that the sponsor would like a list of the animal numbers from those animals with endometrial polyps and sarcomas which were used in the calculations. She asked for clarification on which sarcomas the Cancer Assessment Committee included in its analysis. Dr. Hauswirth replied that we had combined the stromal cell sarcomas with the polyps and had used the revised data which the sponsor had just recently submitted. She said she would give Mrs. Birkhead the information on animal numbers. Dr. Settepani mentioned that the sponsor had made new sections of the uterus and had not included four animals from the high dose group.

Dr. Colaianne then discussed the extrapolations used to determine the virtually safe dose. Dr. Colaianne began by saying that the sponsor had all the relevant statistics memoranda for the extrapolations to a virtually safe dose. The Center had used a multi-stage model and applied the Gaylor-Kodell procedure with the Farmer modification. He agreed to supply the literature references for the methodology. A virtually safe dose was calculated for each tumor type, sex, and species using a one in a million risk factor and the upper 95% confidence level. For details, please refer to the HFV-124 memorandum dated August 8, 1984. Dr. Colainne stated that NCTR had run the calculation and asked if there were any questions regarding the numbers, especially the adjusted values for organ consumption. In response to Dr. Theodorides' questions regarding the validity of combining the endometrial polyps and sarcomas, Dr. Colaianne said that although this tumor type gave the lowest virtually safe dose, 26.4 ppb in liver, extrapolation of the tumor data from the histocytic sarcomas in male rats gave a virtually safe dose of 31.2 ppb in the liver, which is not that much different. Dr. Free asked if males and females would be combined for extrapolation of the histocytic sarcoma data. Dr. Colaianne answered that according to the Center's policy the data from males and females would not be combined for the extrapolation. Dr. Settepani added that the Center was confident in their decision about the oncogencity of albendazole in part because of the finding that this drug caused a significant increase in more than one tumor in more than one sex and in more than one species.

Dr. Weber then begam a discussion of the analytical methodology for albendazole. The sponsor's regulatory method had been validated at 100-200 ppb although USDA had looked at this method down to the 25 ppb level and it seemed to work fine. However, the sponsor would need a method with a sensitivity of at least 5 ppb for the marker in order to monitor for total residues of albendazole at approximately 26 ppb in the liver. Initial residue work by the sponsor showed this was the mean value for total residues of albendazole at 180-day withdrawal after dosing with 10 mg/kg drug. The sponsor agreed with these values. Dr. Weber said he was unaware of a validated regulatory method with a sensitivity of 5 ppb. He was also unclear as to which method the sponsor had used in their studies measuring the proportion of residue marker to total residue.

Dr. Wishousky said that the revised method had a sensitivity of 2.5 ppb. They had validated the method with the USDA at 200 ppb for a regulatory purposes because this was the projected tolerance, but the sponsor had recently submitted results with some validation data to support the 2.5 to 5 ppb claim for their method. When questioned about the sensitivity of the confirmatory methodology, Dr. Wiskousky stated that they had submitted Mass Spectroscopy data down to 12 ppb when monitoring for 6 ions (3 for the marker and 3 for the internal standard). If only 3 ions were monitored or if the amount of liver tissue used was increased from 2.5 to 5 gms, then he felt that the sensitivity of the confirmatory method would be doubled to achieve approximately 5 ppb. Mrs. Birkhead passed out some residue data (see Attachment II). She said that the data submitted in early 1984 on the proportion of albendazole marker to total residue was generated using the same method that was validated by USDA and added that some of Dr. Weber's questions were the same as the reviewer's when she looked at the data but the sponsor had been able to clear up these points.

Dr. Weber said it appeared that the sponsor might have a regulatory method capable of measuring down to 5 ppb but the agency would have to review the protocol in detail before making any final conclusions. He added that the residue data on three animals submitted by the sponsor showed two of the three had residue levels above 5 ppb at 180 days. A statistical extrapolation of this data using the tolerance limit approach (99th percentile of the population with 95% confidence) would give a withdrawal time longer than 180 days. Dr. Settepani asked if the sponsor had any other data at 180 days withdrawal. Dr. Wishousky indicated that they did not. He added that the sponsor was more than willing to work with the USDA to validate this method at 5 ppb and said that 8-12 samples could be analyzed per day per person.

The next topic of discussion was the potential misuse of albendazole under the emergency INADs. Mr. Dykstra began by saying that the agency has always been concerned about widespread use of investigational drugs. These concerns were present in 1979 when the emergency INADs were first implemented, but the agency had agreed that there was an emergency need for a flukicide which called for a limited distribution of albendazole. The sponsor was sent two letters in 1979 (Attachment III) which outlined what the response would be if significant safety questions arose or if the system of monitoring and controlling albendazole's uses broke down.

In 1982, the Center began to see a breakdown in this system. At this time, the Center met with the firm to discuss the situation and also sent a strong regulatory letter to the veterinarian involved. The Center has recently monitored more closely the situation with albendazole.

The Center has put assignments out in the field to investigate the use of albendazole under the emergency INADs. The Center has documented evidence that the following things are occurring:

(1) Veterinarians were not identifying treated animals. This has been an ongoing problem.

(2) The required pre- and posttreatment forms were not being filled out or were inadequately being filled out. Adverse reactions were not being reported and veterinarian prescriptions were inadequate.

(3) Albendazole was being used in goats and other unapproved animals.

(4) Albendazole was being shipped to unapproved areas.

(5) The drug was being promoted in an overzealous manner which could lead to uses other than for the treatment of flukes.

(6) The biggest concern is the documented case of albendazole being used in dairy cows. The current labeling prohibits use in lactating animals. Drug is also being shipped to feedlots where it is unlikely from the weight of the treated animals that a 180-day withdrawal time is being observed. The conclusion of the Center is that the situation of emergency marketing is out of control and there is great concern about human health risks involved.

Mrs. Birkhead asked about how recent the information was concerning the pre-and post treatment forms not being filled out properly. Since last November, her office has been monitoring these forms and they have been returning them to the veterinarian if they are not filled out properly. The firm is also using only one form now. Mr. Dykstra said that all of this information was a result of his office's most recent assignments. Mrs. Birkhead replied that her office began monitoring these forms only six months ago and, since they report to the FDA at quarterly intervals, the Center may not be aware of the steps the firm has taken to correct this problem.

Mr. Hinnah said that the firm is unaware of most of the misuses listed by Mr. Dykstra. However they had made recent modifications in their monitoring system to ensure greater control of alberdazole distribution. Distribution is presently handled by the ten branches under Standard Operating Procedures which have been in place for four years. Mr. Hinnah is aware of a couple of shipments to unauthorized states but these problems were picked up and corrected. Dr. Settepani asked if their system would detect if a veterinarian had the drug dropped at a feedlot but was given no clear answer.

Dr. Hinnah stated that these branches have made a special effort to ensure that the veterinarian is aware of the restrictions on use of albendazole. The treatment forms are sent to Mrs. Birkhead, whose office reviews them and then forwards one copy to the agency. The sponsor had received FDA concurrence before changing the form.

Dr. Hinnah said if the sponsor becomes aware that a veterinarian is not complying with the conditions of use of albendazole, they stop distribution to him. This has occurred with perhaps three or four veterinarians. The sponsor's perception of the situation is that they were aware of recent FDA inspections and also the compliance site inspections at Applebrook and Lincoln, but since they were not notified of any discrepancies, they thought that the FDA was satisfied. However, the firm is willing to take steps to alleviate any perceived problems.

Mr. Dykstra said that in 1979 the agency took the position that they had a shared responsibility with SKAHP to monitor for misuse. The Center's biggest concern is the uses in dairy farms (with dairymen saying that they have no knowledge of milk discard times) and feed lots where it is unlikely that animals are kept for 180 days. Mr. Hinnah replied that an animal might be put in a feedlot at a young enough age to require 180 or more days of growing out if grain was cheap: however this was not the usual case. He estimated that just under a million doses of albendazole are being distributed yearly.

Dr. Norcross asked if the sponsor had any idea if farmers and veterinarians were complying with the 180-day withdrawal time. Mr. Hinnah replied that, with a regulatory method, we will be able to monitor for residues, and this will force the users to comply. He said at the present veterinarians use the forms to identify herds and not individual animals. However, he doesn't believe the drug is going to many (if any) feedlots.

Mrs. Birkhead said that in most of the areas where albendazole is being used, the slaughterhouses routinely eliminate the livers and kidneys because they are not equipped to handle them. Also, a lot of these organs are exported to other countries. She added that meat from brood cattle culled from herds are usually being sold to fast food chains and then distributed throughout the country rather than staying in local areas.

Dr. Settepani asked about promotional ads by the firm which say that albendazole is a broad-spectrum anthelmintic. Mr. Hinnah replied that due to concern over such ads, the firm has stopped distributing promotional material. Mr. Dykstra asked if Dr. Armstrong was still promoting the product and Mrs. Birkhead replied that he was not.

Dr. Norcross asked if the reasons to use a flukicide was to preserve the liver or to increase growth rate. Dr. Theodorides explained the life cycle of a liver fluke and then stated because the fluke lives on blood, it interferes with the nutritional status of the animal. Therefore, it will affect growth; the liver is usually still condemned because it still contains immature flukes (the drug only kills adult flukes) and because it is also damaged by the flukes

Dr. Norcross then asked the sponsor for their thoughts on what we should be doing to correct the problems with misuse of albendazole. Mr. Hinnah replied that the sponsor could be more aggressive in monitoring veterinarians to assure compliance with the withdrawal times. He felt that the key document was the treatment form. He proposed sending these forms to their Lincoln office where the shipping records are kept and checking to make sure veterinarians are accounting for all the drug that they receive. He also thought that the sponsor should outline some course of action such as auditing the veterinarian if they were not complying with the restrictions on albendazole use.

In addition Mr. Hinnah proposed doing random audits of all veterinarians using albendazole and reporting the results to the FDA. He was not sure if this would include identifying the herds treated by veterarians who were not complying with the restrictions.

Mr. Hinnah also suggested modifying the treatment form so that the owner of the animals would retain a copy. Mr. Dykstra said that the owner could be required to present the form at the slaughterhouse but Mr. Hinnah felt that this would be unpractical because there was a single form for the entire herd and individual or subgroups of animals were often culled out for slaughter at any one time.

The last two suggestions by the sponsor were to instruct all their salesmen as to the conditions of use of albendazole, rather than just those in the authorized states, and to emphasize (by drawing a box around them) the warnings on the label against use in veal and dairy cattle.

Two options which the sponsor had considered were either liver discard with a shortening of the withdrawal time or lengthening the withdrawal time. The first suggestion would require identifying the animals but a shorter withdrawal time would mean it would be easier to maintain identification of treated animals. The second proposal would make it more difficult than it is now to ensure compliance.

Mr. Dykstra said the solution to these problems would have to be something agreeable to both USDA and the FDA. Dr. Settepani added that we cannot give the sponsor an answer right now as to which of their suggestions we would consider. However if we institute many changes in the emergency INADs, the Center should probably publicize the fact that we are doing so because we have safety concerns about the product. Mr. Hinnah suggested saying that these changes were made because of misuse of the product rather than safety questions. Dr. Settepani said that should our position about the safety concerns regarding albendazole prevail, we would leave ourselves vulnerable to later criticism that we kept quiet on our safety concerns. Mr. Dykstra added that the Center has gone out on a limb to allow widespread use of this product and now that there are problems, we must take a very conservative approach to solve the problem. Mr. Hinnah stated that SKAHP did not want to be perceived as marketing a carcinogen. He passed out a handout concerning their present and proposed emergency INAD procedures. (see Attachment IV)

Dr. Norcross closed the meeting by saying that Dr. Settepani will be the contact person for the agency. Mrs. Birkhead will be the contact person for the sponsor. Dr. Norcross said he wanted to impress upon the firm the extreme importance of the issue. The Center understands the sponsor's feelings in the matter but the firm will also have to be aware of the Center's position and responsibilities. He said that the Center representatives present at this meeting will meet in the afternoon and decide upon the recommendation to be made to Dr. Crawford. He urged everyone to maintain confidentiality in the matter. Mrs. Birkhead said she would like to emphasize that what the firm had put together was an initial response. They would be open to any suggestions by the Center and are very willing to cooperate with Center representatives.

The meeting ended cordially.

Suzanne C. Fitzpatrick

Suzanne C. Fitzpatrick, Ph.D.

Dr. CRAWFORD. I believe this is—we'll check the records to see what response we made to the memorandum in 1982, but as Dr. Guest mentioned, each time we ordered a staff analysis of the albendazole situation, based on field reports, we made what we believe to be an appropriate response.

Mr. WEISS. Well, again, we would appreciate whatever specific information you can give us as to what kind of followup efforts were undertaken.

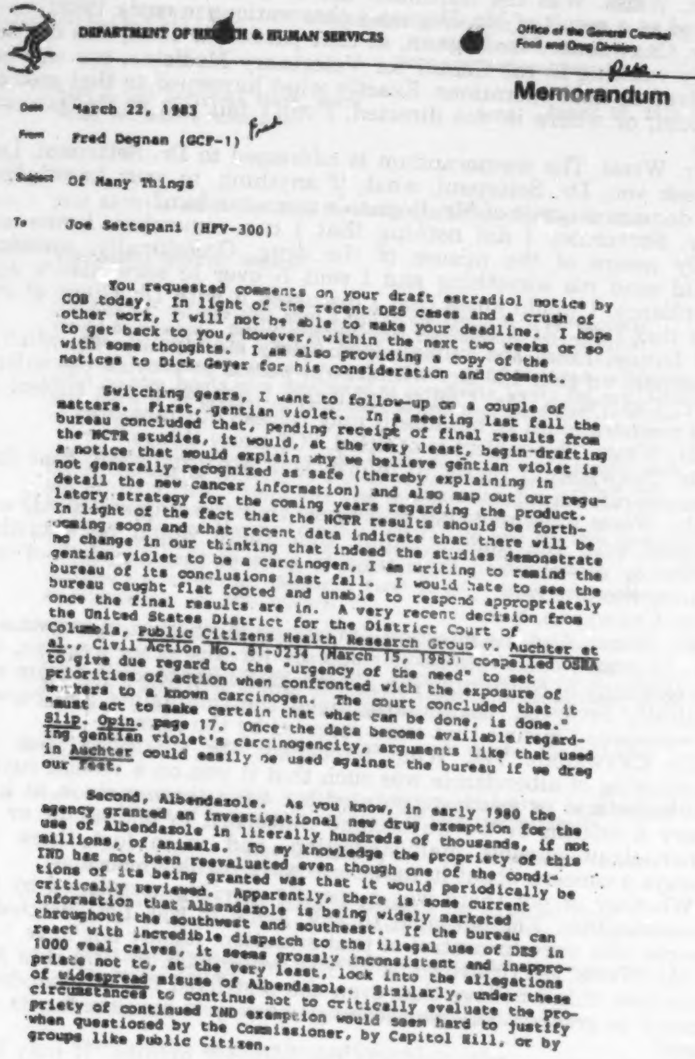
[The information requested follows:]

We do not have additional information, other than documents provided to the subcommittee.

Mr. WEISS. On March 22, 1983, Mr. Degnan wrote:

> [I]n early 1980 the agency granted an investigational new drug exemption for the use of albendazole in literally hundreds of thousands, if not millions, of animals. To my knowledge the propriety of this emergency INAD has not been reevaluated even though one of the conditions of its being granted was that it would periodically be critically reviewed. . . . If the Bureau can react with incredible dispatch to the illegal use of DES in 1,000 veal calves, it seems grossly inconsistent and inappropriate not to, at the very least, look into the allegations of widespread misuse of albendazole.

[Mr. Degnan's March 22, 1983, memorandum follows:]



DEPARTMENT OF HE[illegible]TH & HUMAN SERVICES

Office of the General Counsel
Food and Drug Division

Pete.

Memorandum

Date March 22, 1983

From Fred Degnan (GCF-1) Fred

Subject Of Many Things

To Joe Settepani (HFV-300)

You requested comments on your draft estradiol notice by COB today. In light of the recent DES cases and a crush of other work, I will not be able to make your deadline. I hope to get back to you, however, within the next two weeks or so with some thoughts. I am also providing a copy of the notices to Dick Geyer for his consideration and comment.

Switching gears, I want to follow-up on a couple of
matters. First, gentian violet. In a meeting last fall the
bureau concluded that, pending receipt of final results from
the NCTR studies, it would, at the very least, begin drafting
a notice that would explain why we believe gentian violet is
not generally recognized as safe (thereby explaining in
detail the new cancer information) and also map out our regu-
latory strategy for the coming years regarding the product.
In light of the fact that the NCTR results should be forth-
coming soon and that recent data indicate that there will be
no change in our thinking that indeed the studies demonstrate
gentian violet to be a carcinogen, I am writing to remind the
bureau of its conclusions last fall. I would hate to see the
bureau caught flat footed and unable to respond appropriately
once the final results are in. A very recent decision from
the United States District for the District Court of
Columbia, Public Citizens Health Research Group v. Auchter et
al., Civil Action No. 81-0234 (March 15, 1983) compelled OSHA
to give due regard to the "urgency of the need" to set
priorities of action when confronted with the exposure of
workers to a known carcinogen. The court concluded that it
"must act to make certain that what can be done, is done."
Slip. Opin. page 17. Once the data become available regard-
ing gentian violet's carcinogencity, arguments like that used
in Auchter could easily be used against the bureau if we drag
our feet.

Second, Albendazole. As you know, in early 1980 the
agency granted an investigational new drug exemption for the
use of Albendazole in literally hundreds of thousands, if not
millions, of animals. To my knowledge the propriety of this
IND has not been reevaluated even though one of the condi-
tions of its being granted was that it would periodically be
critically reviewed. Apparently, there is some current
information that Albendazole is being widely marketed
throughout the southwest and southeast. If the bureau can
react with incredible dispatch to the illegal use of DES in
1000 veal calves, it seems grossly inconsistent and inappro-
priate not to, at the very least, look into the allegations
of widespread misuse of Albendazole. Similarly, under these
circumstances to continue not to critically evaluate the pro-
priety of continued IND exemption would seem hard to justify
when questioned by the Commissioner, by Capitol Hill, or by
groups like Public Citizen.

Mr. **Weiss**. Was the continued use of albendazole critically reviewed as a result of Mr. Degnan's observations in early 1983?

Dr. **Crawford**. Mr. Degnan, at that particular time, was not actually working in the Center for Veterinary Medicine, nor was he involved in field operations. Exactly what happened to that memorandum, or where it was directed, I can't tell you at the present time.

Mr. **Weiss**. The memorandum is addressed to Dr. Settepani. Let me ask you, Dr. Settepani, what, if anything, to your knowledge, was done as a result of Mr. Degnan's memorandum?

Dr. **Settepani**. I did nothing that I can remember. I was not really aware of the misuse of the drug. Occasionally, someone would send me something and I sent it over to surveillance and compliance. I would guess that I discussed it with Dr. Guest at the time that I got Mr. Degnan's memorandum.

If I may. From the human food safety standpoint, we relied a great deal on that 180-day withdrawal period to provide the safety.

Dr. **Crawford**. Mr. Chairman, could I ask what the subject of that memorandum is, because it may refresh our memory.

Mr. **Weiss**. The subject is entitled, "Of many things."

Dr. **Crawford**. I regret to inform you, Mr. Chairman, that that does not refresh my memory.

Mr. **Weiss**. I assume that you agree that the original INAD was granted with the understanding that there would be a critical review or reevaluation from time to time of the propriety of continuing the program.

Dr. **Crawford**. Yes.

Mr. **Weiss**. And the question I'm asking is whether in response to Mr. Degnan's observations in 1983, or for any other reasons, the adviseability of continuing the albendazole emergency program was critically reviewed, particularly given the complaints and reports of widespread misuse that were received by the agency.

Dr. **Crawford**. Yes. What happened, Mr. Chairman, was the monitoring of albendazole was such that it was on a virtual continual basis, and as you have pointed out from these memos, at least every 6 months or so, we became concerned in one sector or another about possible maldistribution, and so in fact there was always a concern about it, and there were regular meetings.

Whether or not there was a specific meeting occasioned by this memorandum, I'm not able to say, since it was not directed to people who were in control of that situation, it may not have been.

Mr. **Weiss**. Dr. Crawford, were you aware back in 1979 that FDA scientists didn't believe that even the restricted use of albendazole should be granted because there was no way to monitor for its residues?

Dr. **Crawford**. That was not the majority opinion. It may have been a minority opinion to that effect.

Mr. **Weiss**. In an August 16, 1979, memorandum, Dr. T.S. Sulkowski, Food Additive and Animal Drug Chemistry Evaluation Branch, wrote that his group did not believe that even a restricted approval of albendazole should be granted, in part because, "[t]here is at present no regulatory method that could monitor" for albendazole residues.

[The memorandum referred to follows:]

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Food Animal Additives Staff, HFF-6
Attn: Dr. Robert Scheuplein

DATE: August 16, 1979

FROM : Food Additive and Animal Drug Chemistry Evaluation Branch, HFF-148

SUBJECT: Albendazole Approval Request

DCH does not believe that even a restricted approval of albendazole should be granted. Beyond the fact that considerable toxicological issues remain and that a final tolerance has yet to be established, the chemical requirements are far from being met. Even if 10 ppb or 100 ppb total residue levels were considered as acceptable levels for restricted use, there is at present no regulatory method that could monitor either of the levels.

The 10 ppb or 100 ppb total residue levels in muscle would equate, with use of consumption factors, to a total residue level of 20 ppb or 200 ppb in cattle liver. There have been no total residue depletion studies to either of these levels. Consequently, the acceptability of the marker residue and the required assay sensitivity have not been demonstrated. The last depletion day for which we have any information on total residues or the proposed marker is day 40 post medication, at which time total residues are 340 ppb and the marker level 40 ppb. These levels cannot be extrapolated for NADA approval.

The firm's proposed determinative assay has not been validated at any level in the governmental laboratories. Additionally, we note that there exists no confirmatory assay for albendazole at any level. Lastly, the firm's metabolism studies to identify albendazole metabolites, which may be of equal or greater concern, are incomplete.

Even a restricted approval of albendazole would require the following studies:

1. Acceptable metabolism studies to identify metabolites of albendazole in tissues of both cattle and toxicity test species/strain.
2. A total residue depletion study in the range of whatever level is considered toxicologically acceptable.
3. Studies in the latter range to determine the acceptability of a marker residue and the required assay sensitivity for the marker.
4. Development of both a determinative and a confirmatory assay for the marker residue.
5. Validation of the methods in the governmental laboratories.
6. Field studies to determine a withdrawal period.

For your information, we have attached two earlier memoranda which address the issue of the approval of albendazole.

T. S. Sulkowski

T. S. Sulkowski, Ph.D.

Dr. **Crawford**. I believe at this point, it might be useful, with your permission, to ask Dr. Settepani to comment on the method at that time?

Mr. **Weiss**. Of course. Dr. Settepani?

Dr. **Settepani**. As this problem and what approaches we could take to meeting it evolved, there were many people, Dr. Sulkowski is a petition reviewer, who said, no conditional approval, no emergency authorization, no nothing. You know, they were presenting those viewpoints strictly from the basis of human food safety.

When the decision was made at higher levels to have an emergency authorization as the best way to address this problem, the original letter from Mr. Sherwin Gardner to the sponsor, said that animals would be—a way would be found to identify animals and this clearly put the authorization in our INAD format. What we usually do for an INAD, where the animals are identified as investigational animals when they go to slaughter, they must show the USDA veterinarian in the slaughterhouse, here's an investigational animal.

Here's the drug that it was given; here's the withdrawal time; here are the dates that it was given the drug. We had the added assurance that we could go check the veterinarian's record; here's the veterinarian and when he gave these drugs to the animal, and so on. That's the tightest control that you can have.

To my knowledge, we have never required, or even had a method to monitor for investigational drug residues. So we, from the human food safety viewpoint, as long as we have 180-day withdrawal period, and as long as we were getting no data from the firm, that showed that that 180-day withdrawal period would not be long enough, we were satisfied that we were not putting the public at risk with this emergency authorization.

Mr. **Weiss**. A February 25, 1982, CVM letter to the sponsor states that granting of the emergency INAD "was contingent upon the development of a regulatory method."

[The letter referred to follows:]

Clear file
Albendazole

HFV-300

INAD 1641
INAD 1732

Helen H. Birkhead
Manager Regulatory Affairs
SmithKline Animal Health Products
One Franklin Plaza
P.O. Box 7929
Philadelphia, Pennsylvania 19101

FEB 25 1982

Dear Ms. Birkhead:

We refer to your submission dated June 15, 1981 which was submitted under INADs 1641 and 1733, involving the human food safety aspects of the emergency marketing of albendazole as a flukicide in cattle and sheep. This submission contained modifications to the regulatory method as well as numerous other responses to BVM's letter dated April 6, 1981.

We have reviewed that part of this submission regarding modifications to the proposed regulatory method. The following comments completes our response to this submission and supplement our comments which were transmitted in the Food Animal Additives Staff (FAAS) memorandum dated December 9, 1981. This memorandum was enclosed with our letter dated December 29, 1981.

Because albendazole is being used under the Emergency INAD to treat liver flukes in cattle and sheep in the endemic regions, Food Safety Information Service, United States Department of Agriculture (FSIS/USDA) has been trying to validate the HPLC method that is to be used on an interim basis for the determination of albendazole residues in cattle tissue.

Conclusion:

We concur with FSIS/USDA's conclusion that the proposed regulatory method is unacceptable for the determination of albendazole residues in the 50 to 100 ppb range in cattle liver.

The deficiencies in the method are:

Time per sample - The length of time to perform the method on only a few samples is excessive.

Laboratory safety - The use of ether in the centifugation procedure is hazardous.

Background Interference - HPLC chromatograms of tissue extracts produced by the method show background interference. The sample clean-up procedure is inadequate to separate the marker compound from other components of the extract (see attached chromatograms for details).

Recovery - Recoveries are poor; about fifty percent.

In addition, your recent modifications were not new revisions but had been employed in the demonstration and INAD method validation trial and failed to correct problems.

Because granting of the emergency INAD was contingent upon the development of a regulatory method, we are concerned about the method being unacceptable.

To maintain the emergency INAD status for albendazole, you must develop a regulatory method or be in the process of developing a viable method to monitor for the residues of albendazole in tissues. Having a viable regulatory method is particularly important because of the persistence of these residues.

Please advise us as to your course of action to resolve these problems. Both USDA and FDA would be willing to provide guidance in the development of an alternate method or in the implementation of significant revisions to the current method.

Sincerely yours,

William D. Price, Ph.D.
Chief, Metabolic Products Branch
Division of Drugs for Ruminant Species
Bureau of Veterinary Medicine

Mr. Weiss. When was an acceptable and practicable regulatory method for detecting albendazole residues in meat available to USDA? Dr. Settepani.

Dr. Settepani. What happened was we never got a method to check the 180-day withdrawal period, because residues were at such a low level at that time that we never got a method that was sensitive enough. What happened is in the course of the approval, the NADA approval that they were pursuing, the drug's sponsor had to develop a method, and they said, may we develop a method and would you validate it at a level based on all the information that you have so far.

We said, yes, we'll do that and then we'll be able to use it to monitor as well.

So they sent in a method that I believe was sensitive to 200 parts-per-billion of residue. Our chemists worked on it a little bit more, and got it down to—the chemists disagree—25 to 40 parts-per-billion of residues—which we thought would monitor perhaps a withdrawal period of 3 months, so at least we could do that. And that happened in 1984, I believe, the first half of 1984, we validated that method and got it down to the lower sensitivity.

And at that point, we gave it to USDA to begin to monitor. And it's my understanding that they have not found any violations or any over-40-part-per-billion residues with that method.

Mr. Weiss. Because albendazole had not been approved for marketing, was it not FDA's intent to monitor it more closely?

Dr. Settepani. The monitoring all took place in the identification of animals, the controls put on the veterinarian and so on. We did not depend on a method of analysis to monitor.

Mr. **Weiss**. And were they, in fact, able to identify the hundreds of thousands, if not a million or more, animals that received albendazole each year?

Dr. **Settepani**. I don't know that; I can't answer that question.

Mr. **Weiss**. Dr. Guest.

Dr. **Guest**. Yes, sir, Mr. Weiss. They were able to identify them only on the basis of the counties in those States that were authorized to receive albendazole. If you recall, cattle, for instance, in certain sections of Florida and certain sections of Louisiana and certain sections of Texas, and on and on for 17 States. The breeding cattle, the adult cattle were almost all likely to receive the drug. In most cases, breeding cattle do not go to slaughter but in those rare instances, the identification would come merely through a knowledge of location. The individual cattle were not identified.

Mr. **Weiss**. In an August 23, 1984, memorandum to Dr. Crawford, Dr. Marvin A. Norcross, Acting Associate Director for New Animal Drug Evaluation, cited a number of violative practices in recommending that albendazole be removed from the market. The first such violation included on the list is the "failure to identify number and types of animals that were treated."

[Dr. Norcross' August 23, 1984, memorandum is in the record.]

Dr. **Guest**. That's correct, sir. And I think it's consistent with my response.

Mr. **Weiss**. Well, then, let's see if I understand what you are saying. Normally, each and every animal receiving an investigational drug must be identified. In the case of albendazole, however, identification was not done on an animal-by-animal basis, because hundreds of thousands, if not a million or more animals per year received the drug. You simply assumed that all the animals in a particular county or section of a State were receiving albendazole. Is that what your testimony is?

Dr. **Guest**. Yes, sir.

Mr. **Weiss**. I assume that in the normal situation where individual animals receiving a drug are identified, you can test for residues as well as the disease status of the animal.

When you are dealing with all of the breeding cattle in a particular county or section of a State, how do you monitor for the particular animals? Or was that not even suggested or suspected of being done?

Dr. **Guest**. I think the monitoring, I believe, Dr. Settepani pointed out, the monitoring was conceived to be the control mostly to be through the veterinarian's paperwork and through the followup paperwork which would show what animals have been treated. We also took comfort in the fact that albendazole is a drug that's normally used in mature breeding animals treated perhaps once, maybe twice a year in those areas and cattle on range in pasture are gotten up for their normal medications and checking for calving at least once or twice a year.

So, the controls were more in the sense of things other than being able to identify each animal, one by one, as they came to slaughter, yes, sir.

Mr. **Weiss**. So, you were relying on the veterinarians receiving albendazole to submit the so-called pre- and post-treatment forms? Is that the paperwork that you are referring to?

READEX FICHE

Dr. GUEST. In part, yes sir.

Mr. WEISS. And didn't FDA find that many veterinarians did not send in these forms as required?

Dr. GUEST. Over the course of that 4 years, we ran on those situations where that was not happening, and then we would take action to clarify or straighten that out, yes, sir.

Mr. WEISS. To whom were the veterinarians supposed to send the forms?

Dr. GUEST. Officially, those forms were to go to the drug sponsor distribution center to justify the use of the drug. Subsequent to that, they would come into the Food and Drug Administration.

Mr. WEISS. Now, when did the changeover take place?

Dr. GUEST. I'm sorry, sir. I don't understand the question?

Mr. WEISS. Well, let me see if I understand. Are you saying that the veterinarians were supposed to send them to the sponsor for a certain period of time, after which they would send them directly to the Center? Or that the sponsor, after receiving them from the veterinarians, was supposed to then forward them to the Center?

Dr. GUEST. The latter. They were collected by the sponsor and forwarded to the FDA periodically.

Mr. WEISS. Did the sponsor, to your knowledge, routinely check to see that it was receiving all the required pre- and post-treatment forms from the veterinarians?

Dr. GUEST. We found occasion when that system was falling down in certain distribution points. The company I think in all cases, corrected that as the situation occurred.

Mr. WEISS. Well, now, these were not just isolated situations, were they? I mean, it was not rare that a veterinarian was not submitting the forms to the sponsor? You're not suggesting that it was only an occasional lapse, are you?

Dr. GUEST. I'm suggesting that if it was a pattern, it might be in a certain distribution point that might involve several veterinarians, but it was certainly not a pattern throughout the 17 States, to the best of my recollection.

Mr. WEISS. Didn't an August 1980 inspection of the Ft. Worth Distribution Center for Norden Labs, the SmithKline subsidiary that distributed albendazole, indicate that the company's recordkeeping procedures were so deficient that it did not know which veterinarians had received albendazole and should therefore be submitting pre- and post-treatment forms?

Dr. GUEST. Mr. Chairman, I don't remember the Ft. Worth situation specifically, but I'm sure that's correct.

Mr. WEISS. The report of FDA's August 12, 1980, inspection details exactly that kind of information.

[The report referred to follows:]

DATE ASSIGNED: 8/80 PRIORITY: DATE INSPECTED: 8-12-80
KMPL NO: 413
CENTRAL FILE NO.: 1615985 JO/TA: 17 PHONE: (817) 457-4180 GRP:
NAME: NORDEN LABORATORIES, INC STREET: 5637 E. ROSEDALE ST.
CITY: FT. WORTH COUNTY: 439 STATE: TX ZIP: 76112 DISTRICT: DA

ENDORSEMENT

The previous inspection of 7-10-80 was completed in response to the Bureau of Veterinary Medicine/HFV-234 investigation assignment involving Albendazole Oral Suspension for Liver Flukes INAD 2433/2434.

Distribution information was obtained during the previous inspection for HOU-SEC, NOL-DO, and Dallas Districts' use in monitoring the use of Albendazole in TX, Arkansas, and Louisiana under the reference INADs.

The Dallas District investigation of one consignee of this firm, Lubbock Feedyards, Lubbock, TX, disclosed that the consignee did not observe the 180-day withdrawal period for Albendazole. The consulting veterinarian of Lubbock Feedyards who had assisted the grower in obtaining the Albendazole had not completed the Albendazole pre and post treatment forms. The veterinarian indicated that he was not made aware by Norden Laboratories of his responsibilities to monitor the use of the Albendazole.

The current inspection was completed for the purpose of obtaining interstate documentation of the movement of the Albendazole from Lincoln, Nebr. to Lubbock Feedyards and to obtain further information concerning the Ft. Worth distribution center's responsibility in monitoring the use of the Albendazole.

The manager of the Ft. Worth distribution center stated that his only instructions concerning the monitoring of the distribution of Albendazole was to insure that the Albendazole Suspension Order Form was completed prior to shipment of Albendazole to the consignee. The pre and post treatment forms are self-addressed forms bearing a West Chester, PA address of Norden Laboratories. The local distribution center does not routinely receive the completed forms from the veterinarian.

A discrepancy was noted in the distribution center's inventory during the 7-10-80 inspection. This discrepancy has been resolved with the missing 14 gallons of gallons having been distributed to a consignee and the inventory not updated to reflect this.

FOLLOW-UP: Dallas District will complete one additional inspection of a consignee of Albendazole in Texas; i.e., Taylor Cattle and Vet., Canyon, TX. The consignee received 500 gallons of the Albendazole.

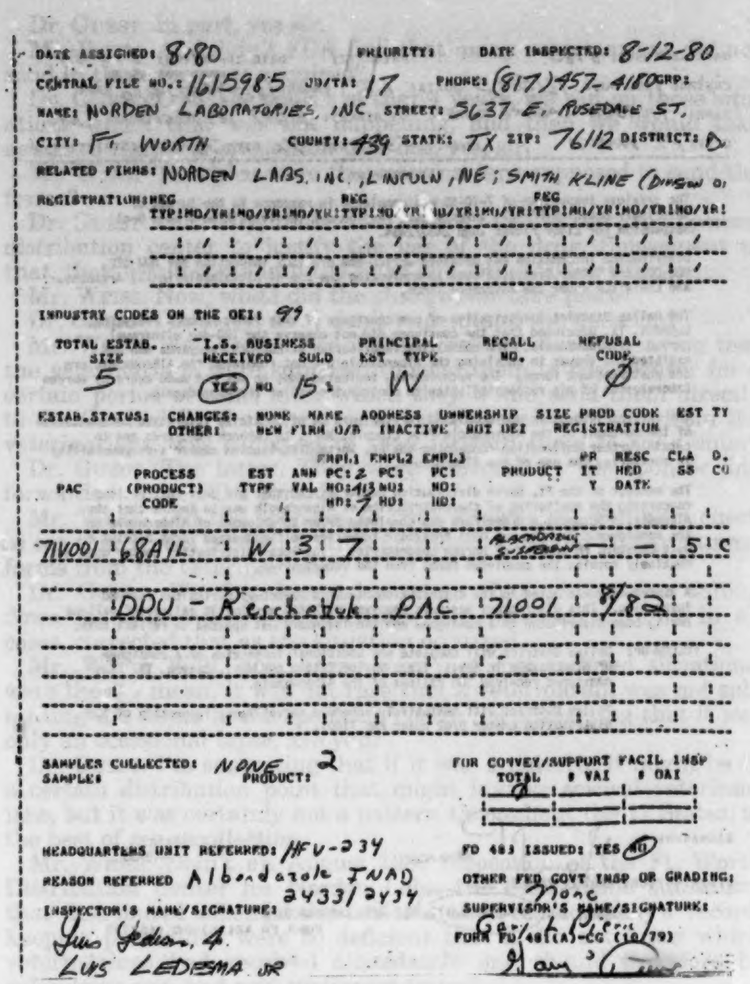
Dallas District will tentatively schedule surveillance inspection of the distribution center 8/82 under PAC 71001.

SIGNATURE Gary L Pierce DATE: 8-19-80

DISTRIBUTION: GARY L. PIERCE, SCSO

O-DAL, KNU, HFV-234/Medill, HLF C/S, Lubbock R.P.

FORM FD 481(C)-CG (10/79)



DATE ASSIGNED: 8/80 PRIORITY: DATE INSPECTED: 8-12-80

CENTRAL FILE NO.: 1615985 JD/TA: 17 PHONE: (817) 457-4180 GRP:

NAME: NORDEN LABORATORIES, INC. STREET: 5637 E. ROSEDALE ST.

CITY: FT. WORTH COUNTY: 439 STATE: TX ZIP: 76112 DISTRICT: D

RELATED FIRMS: NORDEN LABS. INC., LINCOLN, NE; SMITH KLINE (DIVISION OF

REGISTRATION:

REG TYP	MO/YR	MO/YR	MO/YR	REG TYP	MO/YR	MO/YR	MO/YR	REG TYP	MO/YR	MO/YR	MO/YR
	/	/	/		/	/	/		/	/	/
	/	/	/		/	/	/		/	/	/

INDUSTRY CODES ON THE OEI: 99

TOTAL ESTAB. SIZE	I.S. BUSINESS RECEIVED	SOLD	PRINCIPAL EST TYPE	RECALL NO.	REFUSAL CODE
5	[✓ YES] NO	15 %	W		0

ESTAB. STATUS: CHANGES: NONE NAME ADDRESS OWNERSHIP SIZE PROD CODE EST TY
OTHER: NEW FIRM O/B INACTIVE NOT OEI REGISTRATION

PAC	PROCESS (PRODUCT) CODE	EST TYPE	ANN VAL	EMPL1 PC: 2 NO: 413 HD: 7	EMPL2 PC: NO: HD:	EMPL3 PC: NO: HD:	PRODUCT	PR IT Y	RESC HED DATE	CLA SS	D. CU
71V001	68AIL	W	3	7			ALBENDAZOLE SUSPENSION	—	—	5	C
	DPU - Reschedule				PAC		71001		8/82		

SAMPLES COLLECTED: NONE
SAMPLE: PRODUCT: 2

FOR CONVEY/SUPPORT FACIL INSP

TOTAL	# VAI	# OAI
0		

HEADQUARTERS UNIT REFERRED: HFV-234

FD 483 ISSUED: YES [✓ NO]

REASON REFERRED Albendazole INAD 2433/2434

OTHER FED GOVT INSP OR GRADING: None

INSPECTOR'S NAME/SIGNATURE:
Luis Ledesma, Jr.
LUIS LEDESMA JR

SUPERVISOR'S NAME/SIGNATURE:
Gary L. Pierce

FORM FD/481(A)-CG (10/79)

PRODUCT LISTING

CFN: 1615985

EMPL. NO. 413

ESTABLISHMENT NAME: NORDEN LABORATORIES, INC.

DATE INSPECTED: 8-12-80

DATE ASSIGNED : 8 /80

DATE COVERED	PRODUCT CODE	EST TYP	EST TYP	EST TYP	PRODUCT DESCRIPTION
8/12/80	68AIL20	W			ALBENDAZOLE SUSPENSION
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FORM FD 481(C)-CG (10/79)

EIR
Norden Laboratories, Inc.
5637 E. Rosedale St.
Ft. Worth, TX

8-12-80
Luis Ledesma, Jr.
Investigator

SUMMARY OF FINDINGS

This was a limited inspection covering Albendazole Suspension. Inspection was conducted to obtain further information concerning the firm's Albendazole program (This firm is a distribution center for Norden Laboratories, Inc., Lincoln, NE) and to obtain documentation covering the firm's shipment of Albendazole to Lubbock Feedyards, Lubbock, TX (Documentation covering the firm's shipment of Albendazole to Taylor Cattle and Vet, Canyon, TX was also obtained at this time) and to obtain documentation covering the firm's inability to account for 14/1-gallon bottles of Albendazole Suspension during the July 11, 1980 inspection.

On arrival at the firm, credentials were shown to and FD-482 issued to Mr. Richard F. St. Germain, Branch Manager. Mr. St. Germain stated that he is the most responsible individual at the firm in this location. During the inspection, Mr. St. Germain was observed to give orders to at least three of the firm's employees which were observed to be carried out. Mr. St. Germain accompanied me throughout the inspection and was interviewed and provided relevant information; he also provided access to the records copied during the inspection, and at the conclusion of the inspection, signed the affidavit prepared to cover the shipments of Albendazole by the firm to Lubbock Feedyard and Taylor Cattle and Vet. This documentation was submitted separately from the report.

I asked Mr. St. Germain about the firm's responsibility concerning follow-up conducted when Albendazole Suspension Pre-Treatment and Post-Treatment forms were not submitted by veterinarians to whom Albendazole Suspension had been shipped; I also asked him whether the salesmen (specifically a Mr. David Harber) would have any responsibilities to insure that these forms were submitted. Mr. St. Germain stated that they had received no instructions or directions concerning this from either their home office in Lincoln, NE or their office in West Chester, PA (The pre and post-treatment forms should be mailed to the West Chester, PA office). Mr. St. Germain stated that the only instructions which the distribution center had were that an Albendazole Suspension Order Form had to be on file at the distribution center (This form is signed by the veterinarian) before any Albendazole Suspension could be shipped by the distribution center. Mr. St. Germain stated that if a veterinarian called the office or if a veterinarian contacted one of the salesmen concerning Albendazole Suspension, either the distribution center or the salesmen would explain verbally to the veterinarian the requirement for a signed Albendazole Suspension order form to be on hand at the distribution center before any Albendazole Suspension could be shipped and to verbally explain the pre and post-treatment forms which were required to be completed. Mr. St. Germain stated that the Albendazole Suspension order forms could be provided to veterinarians either by the distribution center or salesmen; he stated that the pre and post-treatment forms were included with shipments of the Albendazole Suspension.

The Albendazole Suspension pre and post treatment forms are 3-part forms which Mr. St. Germain stated should be folded over and mailed to the firm's West Chester, PA office (the address appears on the back of the third copy) by the veterinarians. Copies of the pre and post-treatment forms are submitted as Exhibits 1 and 2 of this report. Mr. St. Germain stated that all of the firm's invoices are billed through the firm's Lincoln, NE office (Therefore, the firm's Lincoln, NE office should have records of the firm's distribution of Albendazole), but that he did not know how the firm's West Chester, PA office would receive information on which veterinarians had received Albendazole Suspension and should be submitting pre and post-treatment forms. Mr. St. Germain stated that, if the distribution center received any of the pre and post-treatment forms, adding that some had been received, he would simply forward the forms to the West Chester, PA office. Mr. St. Germain stated that any questions concerning how distribution information was provided to the West Chester, PA office should be directed to Mr. Frank Schrilli, Product Manager, located at the Lincoln, NE office. He stated that Mr. Schrilli's phone number is 402/475-4541. Regarding the salesman, David Harber, Mr. St. Germain stated that he is the firm's sales rep located in Amarillo, TX and that his home phone number would be 806/353-4613; Mr. St. Germain stated that Mr. Harber's Immediate Superior would be Mr. Quentin Bottorf, Regional Manager, located in Columbia, MO (He added that Mr. Bottorf's phone number is 314/449-5436).

ALBENDAZOLE SUSPENSION ACCOUNTABILITY

During the July 11, 1980 inspection, the firm was not able to account for 14/1-gallon bottles of Albendazole Suspension. Mr. St. Germain had not been present during that inspection. Mr. St. Germain stated that, after he had returned and been advised by the Assistant Manager that they had not been able to account for 14 gallons of Albendazole Suspension, he initiated a customer by customer search to determine if a shipment had been made that was not entered on the firm's "running inventory" cards. Mr. St. Germain stated that the firm determined that a shipment had been made to Forgason, Inc., Hungerford, TX on 5-29-80 and that this shipment had not been entered in the firm's inventory cards. A copy of the invoice for this shipment is submitted as Exhibit 3. This shipment is for 16 gallons; the discrepancy of two gallons remaining (on 7-11-80) was apparently caused by an order for 2 gallons having been taken on 7-10-80 which were still physically present at the firm at the time I counted the firm's stock on 7-11-80.

During this inspection, I copied the firm's "running inventory" cards for the Albendazole Suspension; these are submitted as Exhibit 4 of this report. A handwritten number in ink at the upper righthand corner of each card identifies the sequence of the cards submitted in this Exhibit (Some cards had information on both sides and were copied in an order that facilitated copying the cards rather than in sequential order). The 5-29-80 shipment to Forgason, Inc. had not been entered on these cards and was not entered until 7-14-80 (after the 7-11-80 inspection). At the time of the present inspection, the firm's inventory showed 934 gallons of Albendazole Suspension to remain at the firm; a physical count of the Albendazole Suspension in the warehouse disclosed that 934 gallons of Albendazole actually were on hand at the firm.

Luis Ledesma Jr.

Luis Ledesma, Jr.
Investigator

ll:mp:8-14-80

ADDENDUM

The only record the firm had covering the receipt of Albendazole Suspension from the firm's Lincoln, NE plant was a "stock transfer" form; Mr. St. Germain stated that the firm received all shipments from the plant via Graves Truck Lines, Dallas, TX. I visited Graves Truck Lines, Inc., 4356 Singleton Blvd, Dallas, TX on 8-13-80 and contacted Ms. Mary Ledford, Secretary to the terminal manager, who stated that the firm's freight bills are filed by "PRO" number and that we would need more specific information to be able to locate a freight bill at their office. She stated that if only a date was available, they would need the shipping date rather than the receiving date to attempt to locate a freight bill.

Luis Ledesma, Jr.

Luis Ledesma, Jr
Investigator

LL;mp;8-14-80

Mr. **Weiss**. During that inspection, FDA personnel, according to the report, learned that all records on what veterinarians received the drug were kept at Norden, while all completed pre- and post-treatment forms were sent to SmithKline's headquarters in West Chester, PA. As a result, a Norden official conceded that "he did not know how the firm's West Chester, PA, office would receive information on which veterinarians had received Albendazole Suspension and should be submitting pre- and post-treatment forms."

So that more than 4 years before the albendazole program was terminated, FDA knew on the basis of that kind of investigation that the sponsor was not monitoring veterinarian compliance with the requirement to submit pre- and post-treatment forms. Isn't that correct?

Dr. **Guest**. I think, as you said, that was—and I believe I said, that in certain distribution areas, I think they did find a breakdown. I think the primary responsibility that Norden had placed on the distribution centers was that they monitor this particular aspect.

Mr. **Weiss**. According to another report of a November 1983 inspection of the sponsor's headquarters, SmithKline's manager of regulatory affairs stated that: no attempt is made by the sponsor to collate and review pre- and post-treatment forms. FDA, she stated, "had understood this."

[The report of this inspection follows:]

[illegible] 17151 PRIORITY: 1 DATE INSPD: [illegible] PAGE 1
[illegible] .517129 JD/TAR 11 CNTY: 029 PHONE: (215) 647-3900
EMPL NO: [illegible] 2586
[illegible] ANIMAL HEALTH PROD STREET: 1600 PAOLI [illegible]
[illegible] WEST CHESTER STATE: PA ZIP: 19380 DISTRICT: E

ENDORSEMENT

This inspection was conducted by request of HFV-205 for a for-cause inspection of Sponsor/Monitor practices concerning the distribution of the INADA drug Albendazole under an emergency use program identified by FDA as the Special Liver Fluke Program. This investigational animal drug was approved by FDA for limited distribution under strict controls to meet an emergency situation for control of flukes in cattle and sheep.

This firm was previously inspected for compliance with Sponsor/Monitor procedures 3/81 and was classified in compliance. The last inspection at the firm 9/82 was for GMP coverage and that inspection was also in compliance.

Current inspection determined that the firm did not utilize its conventional system for monitoring INADA studies but set up a separate system tailored specifically to the Albendazole program. Responsibility for monitoring the program was designated to personnel at the SKAHP manufacturing plant in Lincoln, NE known as Norden. Only limited information was available at the West Chester, PA facility. No 483 was issued pending Bureau review.

Follow-Up: Refer to Bureau of Veterinary Medicine for evaluation and final classification.

VOLUNTARY CORRECTION DATA

PAC	PROBLEM TYPE	CORRECTIVE ACTION	EST. COST OF ACTION	DATE ACTION VERIFIED	CORRECTING UNIT	REPORTING DISTRICT

SIGNATURE James T Ware 12/13/83 DATE:
James T. Ware, Supervisory Investigator

DISTRIBUTION: O: DPU/Files; cc+exh: HFV-205; c/s: HFO-510, JTW, KRK

FORM FDA 481(E)-CU (09/83)

SmithKline Animal Health Products
1600 Paoli Pike
West Chester, PA 19380
11/15, 17-23, 28-30/83 ALd

SUMMARY OF FINDINGS

This inspection was conducted in response to a request from the Bioresearch Monitoring Staff, HFV-205, for a for-cause inspection of SmithKline Animal Health Products to determine its activities as Sponsor/Monitor of the investigational drug, Albendazole. FDA approved the sale of this investigational flukicide in order to meet an emergency situation for control of adult liver flukes in cattle and sheep but imposed strict conditions for its use and distribution. The firm was previously inspected for compliance with Sponsor/Monitor procedures 5/81 and was classified in compliance. The last inspection at the firm 9/83 was for CGMP coverage and was likewise classified in compliance. (This assignment was conducted simultaneously with a GLP inspection which has been submitted separately.)

The current inspection determined that the firm did not utilize its conventional system for monitoring INADA studies since they felt that the emergency liver fluke program more closely allied itself with their commercial practices rather than their investigational ones. Hence, monitoring of the Albendazole program was designated primarily to personnel at the SKAHP manufacturing facility known as Norden in Lincoln, NE. Only limited information was available at the West Chester, PA facility which is submitted under the Sponsor/Monitor format (CP 7348.810) as requested in the assignment.

HISTORY OF BUSINESS

SmithKline Animal Health Products (SKAHP) is a wholely owned subsidiary of the Smith Kline Beckman Corporation whose headquarters is located at One Franklin Plaza, 1600 Vine Street, Philadelphia, PA 19101. The President and Chief Executive Officer of Smith Kline Beckman is Henry (NMI) Wendt and the President of SKAHP is Norman H. Blanchard. Both Mr. Wendt and Mr. Blanchard are located at the above referenced address.

This inspection was conducted at the SKAHP Applebrook Research Center which serves as the site where research relating to animal health and nutrition is conducted. Some pre-clinical and preliminary clinical trials involving new animal drugs are also conducted at this facility. In addition, the Applebrook Research Center serves as the Quality Control laboratory for SKAHP's medicated premix manufacturing plant located at Lowell, Arkansas. Management is currently developing plans to establish this location as world headquarters for SKAHP.

PERSONS INTERVIEWED AND ADMINISTRATIVE PROCEDURES

This inspection of Sponsor/Monitor duties was conducted in conjunction with a GLP inspection requested by BVM. In relation to this, an FDA 482 and credentials were initially presented on 11/15/83 to Dr. Vasilios J. Theodorides, Manager of Parasitology and Toxicology, of the Applebrook Research Center. The director of the facility, Dr. Brian G. Bagnall, was out of the country at this time.

PERSONS INTERVIEWED AND ADMINISTRATIVE PROCEDURES (Cont'd)

A second FDA 482 and credentials were presented on 11/18/83 to Henry J. vanVeen, Vice President Industrial Products, when it was determined that the organizational structure had recently been changed such that some GLP processes and Sponsor/Monitor duties are now under the direction of the Industrial Products Division of SKAHP. The management of Applebrook and of the Industrial Products Division are totally independent of one another at this location. Refer to the organization chart submitted as Exhibit A.

No FDA 483 was issued at the close of the inspection on 11/30/83 relating to Sponsor/Monitor duties. For details concerning GLP compliance, refer to the EIR submitted under PAC 66808.

All information and records were obtained from Helen H. Birkhead, Manager of Regulatory Affairs and Manufacturing Quality Assurance.

INDIVIDUAL RESPONSIBILITY

According to Helen Birkhead, she is the most responsibile individual for procedures relating to the INADAs and NADAs for Albendazole under the Special Liver Fluke program. She explained that she formerly worked under the direction of Dr. G.C. Scott, Vice President for Applebrook Research and Development, when FDA and SKAHP initially worked out the program for restricted release of the unapproved Albendazole flukicide in 1979. Mrs. Birkhead explained that Dr. Scott has changed positions within the SmithKline Corporation and is no longer involved with Applebrook or with the Albendazole program. She stated that, although she reports to Dr. C. John DiCuollo for her current duties at the firm, she is not under Dr. DiCuollo for issues relating to the Albendazole program. The responsibility above Mrs. Birkhead would channel through the president of SKAHP, Norman H. Blanchard. Mr. Blanchard is located at corporate headquarters identified in this report under History of Business. Mr. Blanchard reports to Mr. Wendt, President and Chief Executive Officer of the SmithKline Beckman Corporation.

CLAIM OF CONFIDENTIALITY

During this inspection Helen H. Birkhead provided copies of two reports of Quality Assurance internal audits as documentation of the firm's efforts to maintain drug accountability. As such, Mrs. Birkhead feels these documents are confidential and she requested that they not be released under FOI. These audits are identified in this report as Exhibits G1, G2, H1, and H2.

CP 7348.810 - SPONSOR/MONITOR COMPLIANCE WITH REGULATIONS

This assignment was conducted at the request of BVM, HFV-205, as a for-cause inspection of SKAHP relating to its Sponsor and Monitoring procedures for the distribution of the unapproved new animal drug Albendazole. In late 1979, FDA and SKAHP entered into a joint agreement to allow restricted sales of this investigational flukicide in order to meet an emergency situation for the control of adult liver flukes in cattle and sheep. Since Albendazole had been in the approved process for some time and since there was no alternate approved drug to treat this disease, a special Liver Fluke Program was initiated to make Albendazole available on an emergency INAD basis.

The assignment from HFV-205 asked that applicable portions of CP 7348.810 be covered. In addition, several other questions were included relating to the firm's distribution system. This report is organized with the Compliance Program format first, followed by comments relating to the specific questions addressed in the assignment.

SPONSOR INSPECTION REPORT

A. Selection of and Directions to a Monitor

According to Helen H. Birkhead, Manager of Regulatory Affairs for SKAHP, the Albendazole program was not handled under the firm's conventional Sponsor/Monitor program since it represented a totally unique situation legally and administratively. She explained that the firm developed an individualized approach to the Albendazole project based on numerous meetings with FDA during which the provisions for this emergency INADA were established. Unlike the normal investigational study, all licensed veterinarians in the designated states (now 17 states) were eligible to receive Albendazole. In accordance with the FDA/SKAHP agreement, each veterinarian was requested to submit to Norden an order form shown as Exhibit B and a pre-treatment form submitted as Exhibit C. A post-treatment form, Exhibit D, was also to be completed by the veterinarian 6-9 months following treatment or upon re-treatment. These forms, along with the educational materials disseminated by FDA and Norden, were the means by which veterinarians were made aware of the investigational status of this drug and the restrictions for its use. Per Mrs. Birkhead, responsibility for monitoring drug distribution and adverse reactions was assigned by SKAHP to management at Norden and its distribution branches since Norden branch offices and field representatives would have the closest contacts with the veterinarians who would be requesting the Albendazole.

Since monitoring of Albendazole is not handled from the West Chester, PA location, Mrs. Birkhead requested that Norden provide a copy of the branch SOP covering the control over the distribution of Albendazole. This SOP was then provided to me by Mrs. Birkhead and is submitted as Exhibit E. Mr. Kent Kirby of Norden also provided a letter addressed to Mrs. Birkhead outlining other systems used to monitor the Albendazole project. A copy of this letter is submitted as Exhibit F.

Further details regarding monitoring procedures would more appropriately be obtained at Norden or its branch offices. Monitoring, per se, is not being handled by Mrs. Birkhead or anyone else at the West Chester, PA location although the pre and post treatment forms are sent to Mrs. Birkhead. She stated that she receives these forms and submits them, as is, to FDA on a quarterly basis. She further stated that no review of these forms is conducted since the veterinarians would be expected to contact Norden via a sales rep or via their WATTS line consultation service long before they would prepare a written treatment form.

B. Assurance of IRB Approval

Not Applicable

C. Ascertaining the Adequacy of Facilities

Not Applicable

D. Test Article Accountability

As explained previously in this EIR, Albendazole accountability is assigned to Norden and its branch offices. Exhibit E outlines the SOP procedure utilized by branch offices which Mrs. Birkhead requested for me from Norden. In addition, Mrs. Birkhead requested some examples of internal audits of Albendazole distribution to demonstrate how Norden monitors its branches. Exhibits G and H are copies of two internal memos dated 8/24/82 and 8/26/82 respectively describing the results of two telephone audits. Because of discrepancies during the telephone audits, an on-site audit was conducted and the results of this audit are shown in Exhibit I dated 12/6/82.

Additional details regarding test article accountability would more appropriately be obtained from Norden or its field offices. Test article accountability is not handled by personnel at the West Chester, PA facility.

E. Continuing Evaluation of Data

According to information provided by Mrs. Birkhead, case report forms as such were not utilized in the Albendazole project since the distribution pattern was so extensive in comparison to a typical investigational drug program. FDA and SKAHP agreed to require pre and post treatment forms (Exhibits C and D) from each veterinarian in order to meet the requirements of CFR 511.1(b)(8). Mrs. Birkhead stated that they had an agreement with the FDA that SKAHP would not be responsible for monitoring such forms since the paperwork would be voluminous and SKAHP felt that veterinarians would contact Norden via their WATTS consultation service or via a sales representative long before they would mail in such treatment forms if they experienced problems with Albendazole usage. I requested documentation from Mrs. Birkhead of this agreement regarding pre/post treatment forms. Mrs. Birkhead provided a copy of minutes of a meeting between FDA and SKAHP dated 12/4/79 (Exhibit J). In the last paragraph of page 4 and the first paragraph of page 5 some mention is made of these forms but SKAHP's responsibilities in this regard are not stated in this document. Mrs. Birkhead stated that she had no other specific documentation but she emphasized that it was verbally discussed and agreed upon between FDA and Dr. G.C. Scott of SKAHP in setting up the Albendazole program. (Per Mrs. Birkhead, the pre and post treatment forms were later found to be too burdensome and a new form was designed to replace the previous two forms. Exhibit K is a sample of the new form which is gradually phasing out the pre and post treatment forms.)

In terms of reviewing the pre and post treatment forms, Mrs. Birkhead explained that no review is done. The forms are designed to be folded and placed directly in the mail. They are prelabeled as follows "Norden ... P.O. Box 2650, West Chester, PA 19380". Mrs. Birkhead stated that the forms come directly to her where one carbon is filed and one carbon is collected for the quarterly submission to FDA. If the veterinarian inadvertently submits his copy of the form, SKAHP will return it to him explaining the need for the veterinarian to retain this document for his records. No attempt is made to obtain information which is incomplete and no reconciliation with the amount distributed is attempted, per Mrs. Birkhead.

While the general monitoring of the Albendazole program has been assigned by SKAHP to Norden personnel, the treatment forms were designed to be sent to the West Chester, PA facility since SKAHP, per Mrs. Birkhead, never intended to use them as a means of monitoring Albendazole for safety or effectiveness. Again, Mrs. Birkhead was adamant that FDA had understood this.

Since the Albendazole program was unique from its inception and since it more closely resembles commercial distribution patterns, although in a very restricted fashion, Mrs. Birkhead stated that SKAHP felt that monitoring would be best handled through Norden's drug manufacturing complaint handling system. The Norden memo of 12/21/83 (Exhibit F) which Mrs. Birkhead provided to me briefly outlines this system. Basically the Norden sales representative is the main contact with the veterinarian. In addition, Norden maintains a recorded telephone complaint system where veterinarians can obtain assistance or report problems. Per Mrs. Birkhead and this memo, a computer printout of all conversations is made and reviewed for problem areas. Mrs. Birkhead obtained examples of several complaints received by Norden in 1983 regarding Albendazole. These complaints are submitted as Exhibit L, M, and N.

For details concerning this complaint handling system and the role of the Norden salesman, an inspection at Norden would be necessary.

F. Records Retention

Records regarding the Albendazole program are maintained indefinitely per normal record keeping policy of SKAHP.

MONITOR INSPECTION REPORT

Monitoring of the Albendazole program is not handled through the West Chester, PA facility. Any monitoring which is done would be conducted by Norden personnel as directed by management at the Lincoln, Nebraska manufacturing site.

HFV-205 REQUEST FOR INFORMATION REGARDING ALBENDAZOLE

Question No. 1

a) What checking is done at the distribution centers to assure that the veterinarian has completed the required order form?

b) What checking is done to assure that the veterinarian does not practice in an authorized area?

Activities of this nature would be handled by Norden personnel. Refer to Exhibit E for the Norden distribution center SOP covering the handling of Albendazole order forms. Mrs. Birkhead stated that she was not personally aware of Norden's practices in this regard, therefore, a follow-up at Norden would be necessary for additional details.

Question No. 2

a) When are the pretreatment forms completed?

Mrs. Birkhead stated that veterinarians are permitted to stock Albendazole and, therefore, she cannot determine when pretreatment forms are completed.

b) Are all pretreatment forms sent directly to SmithKline by the veterinarians?

c) Are some pretreatment forms collected by the salesmen and sent to SmithKline?

d) Is there any attempt made to match amounts covered by pretreatment forms with the amounts purchased by the veterinarians?

Mrs. Birkhead explained that since the pretreatment forms are self-addressed, she cannot be sure who actually places them in the mail. Again, follow-up at Norden and/or its distribution centers would be more appropriate for this type of information.

Question No. 3

a) Is there any attempt to match pretreatment forms with post treatment forms?

b) Does SmithKline do anything with the forms besides send them to FDA? Do they review the material for adverse reactions?

Per Helen Birkhead, no attempt is made to collate pre and post treatment forms. This, she stated, was agreed upon with FDA. As documentation of this, she provided minutes of an FDA/SKAHP meeting dated 12/4/79 submitted herein as Exhibit J. The first paragraph of page 5 addresses this issue. Likewise, Mrs. Birkhead stated that SKAHP does nothing with these forms except for filing one copy and submitting a copy to FDA on a quarterly basis. Details are covered in this EIR under the heading E. Continuing Evaluation of Data. Summarily, Mrs. Birkhead is firm in her contention that FDA was in agreement with SKAHP that monitoring Albendazole through review of pre and post treatment forms was not necessary. However, specific documentation of this was not available.

Question No. 4

a) What is the role of the Norden salesmen? Do they solicit sales? What promotional material do they have available?

Per Mrs. Birkhead, the Norden salesmen are responsible to inform veterinarians that Albendazole is available and are permitted to "detail" the drug for its approved uses. She explained that they are specifically trained in pathology as it pertains to the use of Albendazole. Salesmen are periodically updated as changes in the Albendazole status occur, she mentioned. Mrs. Birkhead stated that all promotional material available to the Norden salesmen has been FDA approved. No unapproved literature is provided, she stated.

Question No. 5

Obtain copies of all labels, labeling promotional material, and publications, memos to sales force, etc.

Mrs. Birkhead maintains a large ring binder containing Albendazole labeling submissions to the FDA. All literature to be published as well as product labeling carried a cover letter indicating it had been submitted for FDA concurrence.

One submission to FDA on 3/5/82 included labeling for a display box for Albendazole Paste (Exhibit O). This display case, which I photographed (Exhibit P), was later to become the subject of a trade complaint by the Merck Company (Exhibit Q). SKAHP met with FDA on 5/4/83 relative to this complaint (Exhibit Q) and subsequently eliminated the display case entirely as a follow-up to this meeting.

Since all of the information available at this location involves FDA approved promotional materials and labeling, it was not collected at this time. A follow-up at Norden would better determine what material is actually being distributed.

Question No. 6

a) Are they aware of any veterinarian who is not completing the required pre treatment and/or post treatment forms?

b) Have they discontinued shipment to any veterinarian? Who? Why?

c) Are they aware of any veterinarian who is promoting the sales of Albendazole?

d) Are they aware of any distribution houses marketing Albendazole? How did they receive the drug?

Question No. 6 (Cont'd)

e) Have they received any information from any source that the 180 day withdrawal period was not followed?

According to Mrs. Birkhead, all information which SKAHP received concerning the improper or illegal distribution of Albendazole was reported to the FDA. This included such problems as the distribution of Albendazole (Valbazam) from Mexico. Mrs. Birkhead denied any knowledge of veterinarians who are engaged in the sale of Albendazole or of distribution houses which are selling the product. She stated that they would have liked to follow-up on Merck's complaint of OTC Albendazole but Merck, she stated, would not identify the location where such product was purchased.

More information relating to the improper distribution of Albendazole may be available from Norden since they are responsible for drug reconciliation.

Concerning the pre and post treatment forms, Mrs. Birkhead stated that she had no way of confirming whether a veterinarian is or is not completing the forms as required. Only the order forms for Albendazole are being tracted.

Attachments

Copies of 2 FDA 482s; Attachment A of CP 7348.810

EXHIBITS

A - Organizational Chart for SKAHP Applebrook Research Center
B - Photocopy of Albendazole Order Form
C - Pre Treatment Form
D - Post Treatment Form
E - Branch SOP - Albendazole Sales and Distribution
F - Norden memo of 11/21/83 re: Field Reports on Albendazole
G - Norden telephone branch audit of 8/24/82
H - Norden telephone branch audit of 8/26/82
I - Norden on-site branch audit of 12/6/82
J - Minutes of FDA/SKAHP meeting of 12/4/79
K - Revised Albendazole treatment form
L - Albendazole Complaint of 9/12/83
M - Albendazole Complaint of 6/9/83
N - Albendazole Complaint of 2/28/83
O - Albendazole labeling submitted to FDA 3/5/82
P - Photographs of display case for Albendazole Paste
Q - Minutes of FDA/SKAHP meeting of 5/4/83

Ann L. de Marco
Ann L. deMarco
Investigator
Philadelphia District

Mr. WEISS. So we're not talking about random or occasional lapses. We're talking about an entire system that precludes the sponsor and FDA from knowing which veterinarians receiving albendazole were sending in the required pre- and post-treatment forms.

Do you disagree with that paper trail record?

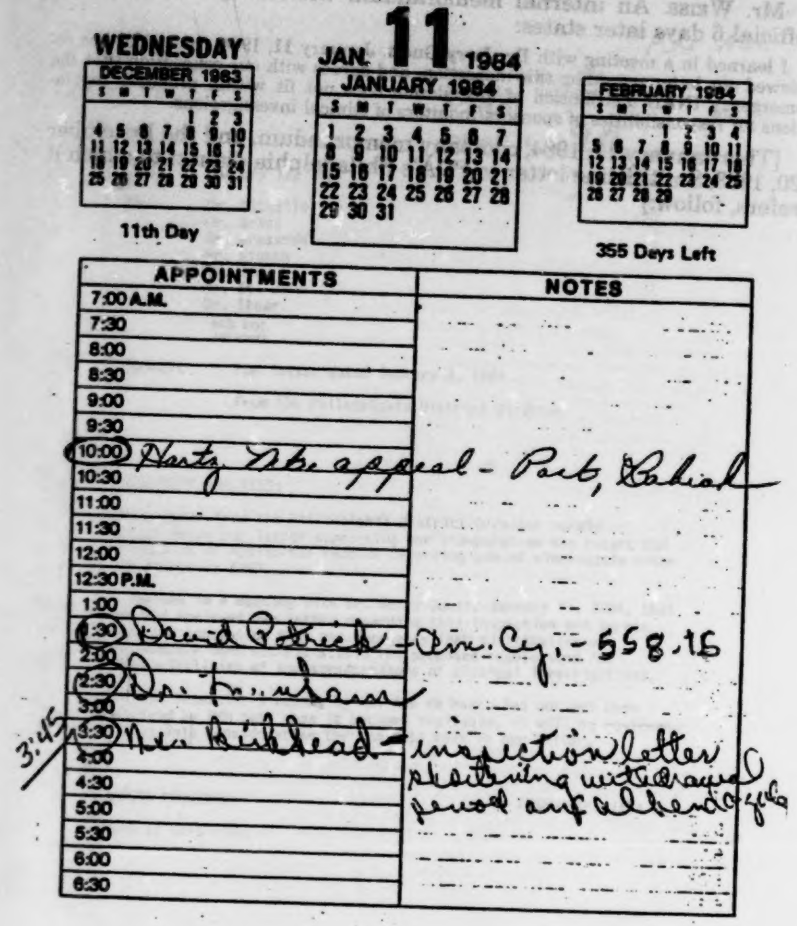
Dr. GUEST. I'm not familiar with the last statements that you read in that memorandum. I don't agree that the system was not working, because it seems to me that the evidence that you have put forward is evidence that we were monitoring the system. And, as I had mentioned earlier, we brought about correction along the way as these things came to our attention.

Mr. WEISS. Dr. Guest, according to a SmithKline memorandum, you met with a company representative on January 11, 1984, and agreed with the firm's contention that it was not required to monitor the use of albendazole. Now do you recall that?

Dr. GUEST. I don't recall precisely. I'm not sure what you're referring to that they weren't required to monitor.

Mr. WEISS. Well, your calendar shows that you were scheduled to meet on January 11, 1984, with Ms. Helen Birkhead, SmithKline's manager of regulatory affairs.

[Dr. Guest's calendar entry for that day follows:]



WEDNESDAY JAN. **11** 1984

DECEMBER 1983

S	M	T	W	T	F	S
				1	2	3
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11th Day

JANUARY 1984

S	M	T	W	T	F	S
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8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

FEBRUARY 1984

S	M	T	W	T	F	S
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19	20	21	22	23	24	25
26	27	28	29			

355 Days Left

APPOINTMENTS		NOTES
7:00 A.M.		
7:30		
8:00		
8:30		
9:00		
9:30		
10:00	Hartz Mtn. appeal –	Port, Kabiak
10:30		
11:00		
11:30		
12:00		
12:30 P.M.		
1:00		
1:30	David Patrick –	Am. Cy. – 558.15
2:00		
2:30	Dr. [illegible]	
3:00		
3:30 (3:45)	Mr. Birkhead –	inspection letter shortening withdrawal period on albendazole
4:00		
4:30		
5:00		
5:30		
6:00		
6:30		

Mr. WEISS. An internal memorandum written by this company official 6 days later states:

> I learned in a meeting with Dr. Jerry Guest, January 11, 1984, that BVM has reviewed our letter regarding this inspection, and agrees with our conception that the emergency INAD distribution of albendazole does not fit within proposed regulations for responsibilities of sponsors/monitors of clinical investigations.

[This January 17, 1984, company memorandum, and the December 20, 1983, SmithKline letter to FDA's Philadelphia district to which it refers, follow:]

File ABZ

Norden Labs, Inc.
Lincoln, Nebraska 68521
2/7-9/84 JAL

Exhibit # 9A

SmithKline Animal Health Products
A SmithKline Beckman Company

DATE: January 17, 1984

TO: Dr. DiCuollo
Mr. Grass
Dr. Grossman
Mr. Hinnah
Mr. Judt
Mr. St. John
Dr. Stear
REG. DOC.
ARCHIVES

SUBJECT: FDA letter dated January 3, 1984
From FDA Philadelphia District Director

REGULATORY ANALYSIS:

This letter from the Philadelphia District Director merely acknowledges our letter supporting our viewpoint on the recent FDA inspection of Applebrook records regarding use of albendazole under the emergency INAD.

I learned in a meeting with Dr. Jerry Guest, January 11, 1984, that BVM has reviewed our letter regarding this inspection and agrees with our conception that the emergency INAD distribution of albendazole does not fit within the proposed regulations for responsibilities of sponsors/monitors of clinical investigations.

The FDA inspector's report by Ms. Ann de Marco has not yet been received by BVM but, when it becomes available, it will be reviewed, taking into consideration the comments made in our letter.

ACTION REQUIRED: **RESPONSIBILITY:**

None at this time.

(i)

A SmithKline Beckman Company

SmithKline Animal Health Products
1600 Paoli Pike, P.O. Box 2650, West Chester, PA 19380 • (215) 251-7400

cable SMITHKLINE PHILADELPHIA
telex 83-4487

December 20, 1983

Mr. L. Y. Johnson
District Director
Food and Drug Administration
Department of Health and
  Human Services
U.S. Customs House, Room 900
2nd and Chestnut Streets
Philadelphia, PA 19106

Dear Mr. Johnson:

As you are aware, our Applebrook Research Center was inspected recently (November 15-30, 1983) under FDA's Bioresearch Monitoring Program. The inspector, Ms. Ann de Marco was cooperative and professional. She made a number of constructive suggestions and, generally, we feel the investigation went very well.

In the course of her investigation, Ms. de Marco asked to inspect our records and interview appropriate personnel regarding the distribution of albendazole under the emergency INAD procedures. This distribution of albendazole as an emergency INAD is a special procedure developed by FDA as a unique drug availability program to address a critical geographical disease problem.

In 1979, the results from a National Cancer Institute study became available which indicated that hexachloroethane, a drug being used by livestock producers for treatment of liver flukes, was a potent carcinogen. This prompted FDA to request action against companies that had been the major suppliers of the drug which essentially cut off the supply of hexachloroethane. To many cattlemen and sheep raisers, this posed a serious economic problem. Death losses in fluke-infested areas can reach 10% or more in a herd. Liver condemnations, feed inefficiency and other economic losses are common in about 25% or more of animals in these areas.

To meet this emergency situation, FDA, in an unprecedented action, formulated very special procedures, under strict conditions, whereby albendazole could be made available in only those states where liver flukes are endemic. Albendazole is still the only drug that has been made available under this unique emergency distribution program; it is an unusual one-of-a-kind situation.

Albendazole is manufactured and distributed under the emergency INAD program by Norden Laboratories, Inc., a wholly-owned subsidiary of SmithKline Beckman Corporation. Norden laboratories uses a totally company-operated distribution system which ensures that their products are under the control of Norden personnel from the time of manufacture until ordered by a veterinarian and shipped to him or her. It is the sales policy of Norden Laboratories to sell to or on the order of graduate veterinarians only. Norden's restricted and company-controlled distribution system weighed heavily in FDA's decision to make albendazole available under the emergency INAD program. The exclusive sales policy of Norden Laboratories, limited to only graduate veterinarians, ensures close and frequent contact between the Norden field and technical services personnel and their clients. Hence the use of albendazole under the special emergency INAD distribution is closely monitored.

Apparently Ms. de Marco was charged to determine our compliance with FDA's proposed sponsor/monitor regulations in connection with the emergency INAD distribution of albendazole. Technically, the pre- and post-treatment forms (and more recently the composite treatment form) completed by the attending veterinarian in connection with the use of albendazole constitute the records to be maintained by the sponsor as required under 21 CFR 511.1(b). Also, the program instituted by FDA and standard procedures formulated and followed by Norden laboratories personnel provide for current monitoring of albendazole use under the emergency INAD. It also provides an excellent framework, as required by 21 CFR 511.1(b)(8), for promptly investigating and reporting to FDA "... any findings associated with use of the new animal drug that may suggest significant hazards pertinent to the safety of the new animal drug", should that occur. However, it is highly inappropriate to attempt to make the unique program established for albendazole distribution under the emergency INAD and the very special procedures developed for control of its use conform to specific procedures proposed to be followed by sponsors and monitors of clinical investigations to "... help assure the quality and integrity of the data filed with the agency pursuant to the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act."

While it is true that albendazole is going through the drug approval process and certain clinical investigations are being conducted to support our New Animal Drug Applications (under Notice of Claimed Investigational Exemption in connection with our various INAD's established for that purpose), the distribution of albendazole under the emergency INAD procedure is unrelated to that effort.

Any data generated in connection with albendazole's use under the emergency INAD program can be considered supportive of its safety and effectiveness under conditions of actual use in the field; however, by no means could that be considered the pivotal clinical investigations conducted to establish its effectiveness for the claims proposed in the New Animal Drug Applications.

SmithKline Animal Health Products and Norden Laboratories, Inc., have had a very close working relationship with the Bureau of Veterinary Medicine during and since the development of the special procedures for distribution of albendazole under the emergency INAD program. We have done everything within our power to ensure that this unique distribution of albendazole is in keeping with the requirements established by FDA as well as with the spirit intended in making the drug available for this special purpose.

Sincerely,

Helen H. Birkhead

Helen H. Birkhead
Manager Regulatory Affairs
SmithKline Animal Health Products

HHB:pm

cc: Dr. Lester Crawford
Ms. Ann de Marco
Dr. Paul Lepore
Dr. Norman Tufts

Dr. GUEST. I'm just not familiar with that, Mr. Chairman. I'd be glad to respond. It may be talking about responsibilities at the veterinarian level and not at the distribution level, because we had agreed, early on, when veterinarians were to be investigated, that the Food and Drug Administration would do that. And that's perhaps the level at which she is talking. I'm just not sure.

Mr. WEISS. Well, would you check, because it appears that this does not merely concern investigations. It involves monitoring distribution and use of the drug, which largely involves monitoring veterinarian compliance with the requirement to submit pre- and post-treatment forms.

So I wish you would check your records and refresh your recollection as to what you told SmithKline concerning this matter?

Dr. GUEST. I'll be glad to, sir.

[The information requested follows:]

There is no indication in any records, all of which the Subcommittee already has, that SmithKline, as sponsor of the albendazole INAD, was relieved of any of the monitoring responsibilities specified under 21 CFR 511.1(b). Two points are clearly reflected by the records, however. In the memorandum of 2/18/80 which specifically addressed the issue of monitoring responsibilities and the field assignment of 4/29/80 it was clear that FDA would monitor only a representative number of veterinarians and producers. This was not to take away from SmithKline's responsibilities but for added assurance. Second, in Dr. Crawford's letter of 12/20/84 one of the reasons given for termination of the INAD was that the firm's monitoring system was inadequate and had failed to control the distribution of albendazole within the requirements of 21 CFR Part 511. Thus it is clear that SmithKline had the monitoring responsibility and that FDA's monitoring was to assure that this was being done properly or, conversely, to show that it was not being done adequately. Admittedly some statements in documents given the Subcommittee are not entirely clear and may have led to misinterpreations by some staff people, but this does not take away from the facts pointed out above.

Mr. WEISS. Dr. Guest, on January 12, 1984, the day following your meeting with a SmithKline representative, a memorandum from CVM's Case Guidance Branch stated that FDA had relieved the sponsor of any responsibility for monitoring the use of albendazole. The memorandum states that, FDA, "not SmithKline," was "responsible for monitoring the veterinarians."

[The memorandum referred to follows:]

B

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Date January 12, 1984

From Case Guidance Branch/HFV-236
Bureau of Veterinary Medicine

Subject 83-331-288 Albendazole
83-331-421 Albendazole
83-321-140 Albendazole

To Dallas District Office/Compliance Branch/HFR-6040
Attention: Gwendolyn Sue Gilbreath

John M. Morton, D.V.M.
d/b/a Morton's Veterinary Clinic
1403 E. Tyler Street
Athens, Texas

Regulatory Letter Approved

We are approving the recommended regulatory letter to Dr. Morton for the illegal distribution of the Investigational New Animal Drug, Albendazole. We are prepared to initiate stronger administrative follow-up if this veterinarian fails to comply with the requirements for distributing new animal drugs. The deciding factor in this case was the undercover purchase by our investigator and the veterinarian's failure to inform the investigator of the extended withdrawal period. Our Human Health Hazard Evaluation Committee is of the opinion that this deviation from the requirements set forth in the Emergency Investigational New Animal Drug procedure is of serious health significance. Albendazole residues present a known teratogenic hazard to animals and possibly to the human fetus.

It is important that a veterinarian have a legitimate doctor/~~patient~~ client relationship when distributing any prescription drug. In distributing Albendazole, the doctor/~~patient~~ client relationship is subject to further stringent control in the form of pre- and post-treatment records. The use of this form offers more assurance that the producer is aware of the withdrawal requirements. Our investigator was not required to sign the pre-treatment form nor was he informed of the withdrawal period.

The rather extended delay in response is a result of the unique circumstances associated with the distribution of Albendazole. We have been researching the history of this emergency INAD to determine what responsibility for these violations must be shared by the sponsor, SmithKline, so we could pursue an orderly regulatory approach. Ordinarily clinical investigator violations would be shared with the sponsor as per 21 CFR 511. After reviewing the applicable emergency INAD files, some personal files, and an internal SmithKline memo, we do not think that SmithKline can be held strictly accountable for their "clinical investigators." Several internal FDA documents indicate that we will be responsible for monitoring the veterinarians not SmithKline. This and other aberrations of the INAD system make it difficult to hold the sponsor accountable for Dr. Morton's actions.

Our Bioresearch Monitoring staff indicates that a NAF letter is ordinarily the first course of action in instituting action against a clinical investigator. However, because of the human health hazard potential of Albendazole, we are of the opinion that a regulatory letter is supportable. Further action would likely be the "Withdrawal of Eligibility to Receive Investigational Use New Animal Drugs." Any clinical investigator subject to withdrawal of eligibility would be offered an opportunity for a hearing pursuant to 21 CFR 511.1(c)(1) and 21 CFR 16. Under the provisions of 21 CFR 511.1(c)(1) the Regulatory Letter will be issued by BVM. Attached is a copy of the regulatory letter to be issued. The District did a commendable job drafting a regulatory letter for such a unique situation; however, it was the position of General Counsel that the letter should cite 511 violations rather than violations of the statute.

Judith Gushee
Consumer Safety Officer

Mr. WEISS. What is the legal authority for relieving a sponsor of all obligations to monitor the distribution and use of an investigational new animal drug?

Dr. GUEST. Mr. Chairman, I think what that refers to is at the veterinarians' level. I think we had agreed early on, with the firm, that if a veterinarian were causing this drug to be mislabeled or go outside of the normal channels in medical practice, that the Food and Drug Administration would look into those matters. The Norden Laboratory, as I recall, was responsible for being certain that the forms were filled out and that the product only went to licensed veterinarians in those areas where the product was authorized for use.

Dr. CRAWFORD. Mr. Chairman, if I may.

Mr. WEISS. Of course Dr. Crawford.

Dr. CRAWFORD. I think what Dr. Guest is referring to there, is that, as we began tightening down on the distribution of albendazole, in response to these periodic lapses that you pointed out, there became some question in the firm's mind as to whether or not they were to deal with what may have been an illegal situation, particularly since, as I mentioned earlier, the Center for Veterinary Medicine and the field forces were cracking down on illegal use of prescription drugs, where did their responsibility to take action against the veterinarians end, and where did ours begin.

I believe the substance of these discussions, which I recall, basically assured the firm that they were not to get into the process of trying to take legal action against the veterinarians, that we were to do that. It was FDA's responsibility in dealing with the civil and criminal penalties that may accrue from misuse of this and other prescription drugs.

Mr. WEISS. Well, we're not even talking in this instance about misuse. What we're talking about is FDA's INAD regulations, which state that a sponsor "shall provide for current monitoring" of an INAD. What that means, as we discussed here, is that the sponsor must keep records of all the veterinarians who receive this INAD drug.

All veterinarians who received albendazole were supposed to submit the pre- and post-treatment forms to ensure appropriate use of the drug. These forms were to enable the sponsor and ultimately FDA to keep track of who was using the drug, whether they were observing the required withdrawal period, and so on.

And again, the memoranda that we've been discussing indicate that the list of veterinarians receiving albendazole was going one place, while the pre- and post-treatment forms were going somewhere else. There was just no way the sponsor could match the veterinarians receiving albendazole with the forms. Nor could it identify what animals were given the drug, how long before slaughter they had received the drug, and so on. It clearly appears from the record that FDA absolved the sponsor of the responsibility to monitor even though the regulations quite clearly state that the sponsor has that responsibility.

And that's what I'm trying to get——

Dr. CRAWFORD. Could we confer on that? Could we confer on that for just a moment?

Mr. WEISS. Please.

Dr. CRAWFORD. Mr. Chairman, the meeting and also the memorandum that you refer to was an attempt to clarify who did what and what unit with CVM was responsible for being sure that those forms were filled out. We did not look upon that as absolving them of their responsibilities.

In terms of what went out to the firm and so forth, I do not believe there was any essential change in our status.

Now, we are going to have to refer back to that memorandum that the drug firm itself had. I wondered if we could get the, I believe you said, January memorandum?

Mr. WEISS. Yes.

Dr. CRAWFORD. And make a response.

Mr. WEISS. This is the January 12, 1984, memorandum to the Compliance Branch of FDA's Dallas district office from FDA's Case Guidance Branch. We will give you a copy of it. It states: "Several internal FDA documents indicate that we will be responsible for monitoring the veterinarians not SmithKline. This and other aberations of the INAD system make it difficult to hold the sponsor accountable * * *"

[This memorandum is in the record.]

Dr. CRAWFORD. OK. Mr. Chairman, we will—with your permission, we will make an analysis of their conclusions. At this point, I do not think—we are confused. I think they mean here that the responsibilities normally expected for sponsor monitor regulations are different for this particular drug.

I assume that they mean that the responsibilities are more stringent. Another interpretation of it, as written, could be that they believe they are absolved of some responsibilities. And, so, we are going to have to respond to that, if we may, for the record.

Mr. WEISS. Well, I wish you could check. I do not see how we can draw the conclusion that you do, but please do check on it.

Do you know if FDA ever advised SmithKline in writing that FDA was assuming total responsibility for monitoring use of the drug and relieving the company of that responsibility?

Dr. CRAWFORD. No; we do not believe that is the case at all.

Mr. WEISS. OK. What we have is a record of internal FDA memorandums and letters from SmithKline to FDA indicating what the firm has been told and it would be helpful if we could find some written record of what FDA advised the firm concerning the responsibility to monitor. So, if you would check your records to see if there is any such record, it would be appreciated.

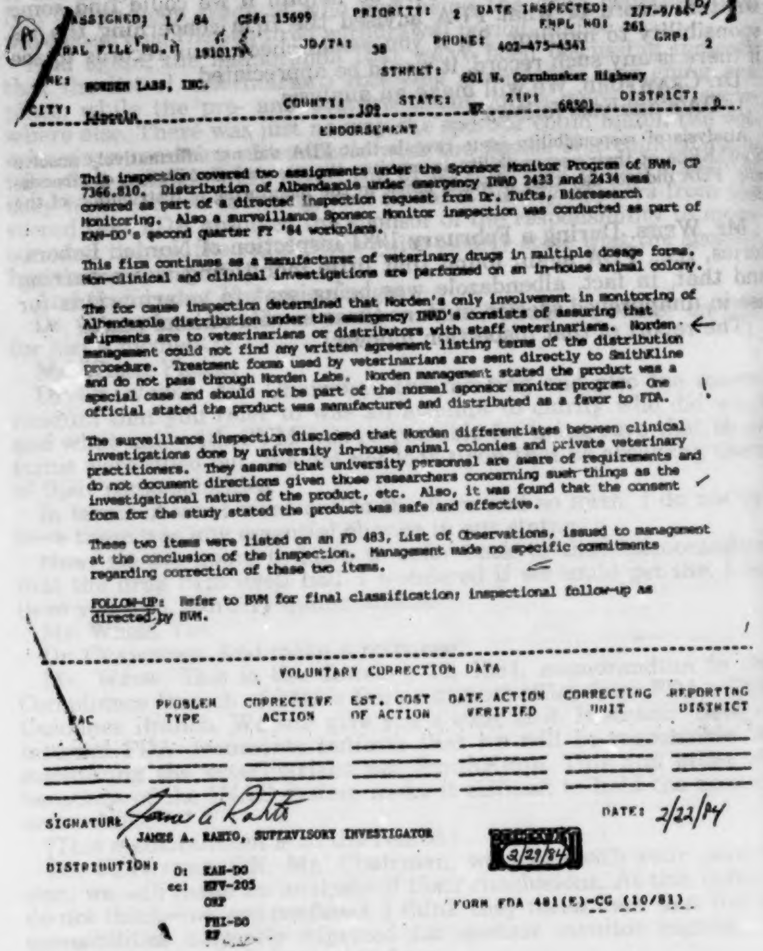
Dr. CRAWFORD. We will make an analysis.

[FDA's analysis follows:]

Analysis of responsibility issue reveals that FDA did not affirmatively absolve SmithKline of their responsibility to monitor the use and distribution of albendazole. FDA did not say that it would assist in the monitoring of distribution of the drug.

Mr. WEISS. During a February 1984 inspection of Norden Laboratories, Inc., FDA again found that little monitoring was occurring and that, in fact, albendazole was being sent to veterinarians for use in unapproved species, such as those in wild animal parks.

[The report of that inspection follows:]



(R) ASSIGNED: 1/84 CS#: 15699 PRIORITY: 2 DATE INSPECTED: 2/7-9/84 (6)
EMPL NO: 261
RAL FILE NO.: 1910179 JD/TA: 38 PHONE: 402-475-4341 GRP: 2
NE: NORDEN LABS, INC. STREET: 601 W. Cornhusker Highway
CITY: Lincoln COUNTY: 109 STATE: NE ZIP: 68501 DISTRICT: 0

ENDORSEMENT

This inspection covered two assignments under the Sponsor Monitor Program of BVM, CP 7366.810. Distribution of Albendazole under emergency INAD 2433 and 2434 was covered as part of a directed inspection request from Dr. Tufts, Bioresearch Monitoring. Also a surveillance Sponsor Monitor inspection was conducted as part of KAN-DO's second quarter FY '84 workplans.

This firm continues as a manufacturer of veterinary drugs in multiple dosage forms. Non-clinical and clinical investigations are performed on an in-house animal colony.

The for cause inspection determined that Norden's only involvement in monitoring of Albendazole distribution under the emergency INAD's consists of assuring that shipments are to veterinarians or distributors with staff veterinarians. Norden management could not find any written agreement listing terms of the distribution procedure. Treatment forms used by veterinarians are sent directly to SmithKline and do not pass through Norden Labs. Norden management stated the product was a special case and should not be part of the normal sponsor monitor program. One official stated the product was manufactured and distributed as a favor to FDA.

The surveillance inspection disclosed that Norden differentiates between clinical investigations done by university in-house animal colonies and private veterinary practitioners. They assume that university personnel are aware of requirements and do not document directions given those researchers concerning such things as the investigational nature of the product, etc. Also, it was found that the consent form for the study stated the product was safe and effective.

These two items were listed on an FD 483, List of Observations, issued to management at the conclusion of the inspection. Management made no specific commitments regarding correction of these two items.

FOLLOW-UP: Refer to BVM for final classification; inspectional follow-up as directed by BVM.

VOLUNTARY CORRECTION DATA

PAC	PROBLEM TYPE	CORRECTIVE ACTION	EST. COST OF ACTION	DATE ACTION VERIFIED	CORRECTING UNIT	REPORTING DISTRICT

SIGNATURE James A. Rahto DATE: 2/22/84

JAMES A. RAHTO, SUPERVISORY INVESTIGATOR

2/29/84

DISTRIBUTION: O: KAN-DO
cc: HFV-205
ORP
PHI-DO
RF

FORM FDA 481(E)-CG (10/81)

EIR
Norden Labs, Inc.
601 West Cornhusker Highway
Lincoln, Nebraska 68501

2/7-9/84
JNL

SUMMARY OF FINDINGS:

This was a for cause inspection under the sponsor monitor program of BVM, CP 7366.810. Distribution of Albendazole under emergency INAD's 2433 and 2434 was covered. Additionally, a surveillance sponsor monitor inspection was conducted as part of BVM's second quarter '84 bioresearch assignments. The firm's was covered under the surveillance assignment.

This firm continues as a manufacturer of veterinary drugs in multiple dosage forms. Non-clinical and clinical investigations are performed on an in-house animal colony and research farm.

The for cause inspection determined that Norden's only involvement in monitoring of Albendazole distribution under the emergency INAD's consists of assuring that shipments are to veterinarians or distributors with staff veterinarians. Norden management could not find any written documents listing their responsibilities. They stated that any agreement with the Food & Drug Administration must be on file at Smith Kline Animal Health Products in Pennsylvania. Treatment forms used by veterinarians are sent directly to Smith Kline Animal Health Products (SKAHP) and do not pass through Norden Labs.

Norden's management was reluctant to allow inspection of Albendazole activities. They stated it was a special case and should not be covered under the sponsor monitor program. One official stated the product was manufactured and distributed as a favor to FDA only. This inspection basically confirmed what was found in an earlier inspection of Smith Kline Animal Health Products by PHI-DO. That is that there is little or no monitoring other than the distribution of the product.

The surveillance inspection disclosed that Norden differentiates between clinical investigations conducted in university animal colonies and those conducted by private practitioners. They assume that university personnel are aware of all requirements and thus do not provide all of the same information about requirements which is furnished to private practitioners. They also conduct in-house clinical investigations which they do not consider clinical trials. Their understanding appeared to be that only investigations conducted by private practitioners came under the regulations pertaining to monitoring activities. Also, it was found that the consent form for the study reviewed stated that the product was safe and effective. These two items were listed on an FD 483, List of Observations, and discussed with management.

HISTORY OF BUSINESS:

Norden Laboratories is a wholly owned subsidiary of Smith Kline Animal Health Products. SKAHP is in turn a division of Smith, Kline & Beckman. President of Norden Laboratories is J.P. Wareham. Exhibit #1 of this report is a chart showing the chain of command for Norden Laboratories. Smith Kline Animal

Health Products is located at 1600 Paoli Pike, P.O. Box 2650, Westchester, Pennsylvania 19380.

This firm continues as a manufacturer of veterinary pharmaceuticals and biologics. In addition the Lincoln facility includes an animal colony in which clinical investigations and non-clinical investigations are conducted.

This firm is currently registered as required by Section 510 of the Act. The last registration date was 7/83.

PERSONS INTERVIEWED AND INDIVIDUAL RESPONSIBILITY:

Upon arrival at the firm I was initially introduced to Robert M. Grossman, Ph.D., Manager, Pharmaceutical Quality Assurance. Dr. Grossman is the primary FDA liaison person for manufacturing operations. He in turn introduced me to Dr. William H. Ray, Ph.D., Manager, Scientific Affairs, Pharmaceutical Development. I presented my credentials to Dr. Ray and issued an FD 482, Notice of Inspection, to him. Dr. Ray reports to George M. Grass, Vice-President of the Pharmaceutical Development Division. Dr. Ray was present on the first day of the inspection. He was not at the firm on succeeding days. Dr. Ray stated that he had responsibilities for operations of non-clinical and clinical investigations. He stated that he was responsible for regulatory aspects of those studies. Dr. Ray's absence from the firm was due to a trip to FDA in Washington concerning new animal drugs and their applications. Dr. Grass introduced me to John Murphy, Manager of Pre-Clinical Studies. Mr. Murphy was previously responsible for monitoring of university clinical trials until sometime in 1983 when his responsibilities changed to the non-clinical area. As part of John Murphy's responsibilities he wrote protocols. In 1983 when Mr. Murphy's responsibilities changed he began reporting to Dr. J.R. Simpson, Manager of Clinical Development, Pharmaceuticals. Formerly Mr. Murphy had reported to Dr. Ray. Mr. Murphy furnished information concerning the Filaribits Plus clinical investigations. He furnished no information concerning Albendazole. Dr. Leland J. Volker is now responsible for monitoring of clinical studies. His title is Manager, Clinical Studies, Pharmaceuticals. Dr. Volker is a veterinarian and his CV is attached as Exhibit #12. Dr. Volker started his responsibilities as clinical studies monitor when John Murphy switched to the pre-clinical study area.

Dr. Douglas A. Armstrong, D.V.M., was previously responsible for monitoring clinical trials conducted by private practitioners. At the time that Dr. Armstrong monitored trials for Norden he was a private consultant not actually employed by Norden. He had previously worked for Smith Kline in the same field. He monitored trials for Norden from 1980 to 1983. Dr. Armstrong's CV is attached as Exhibit #13 of this report. Dr. Armstrong monitored field trials by private practitioners of the product. I was introduced to Dr. Armstrong but he furnished no information for this report.

Dr. J.R. Simpson is Manager of Clinical Development, Pharmaceuticals. John

Murphy and Leland Volker currently report to J.E. Simpson who in turn reports to George Grass, Vice-President. I was introduced to Dr. Simpson but he did not furnish any information for this report. Dr. Simpson and Dr. Volker both stated that they were new to their positions having started sometime in 1983 and neither appeared to have much knowledge concerning operation of the clinical trials and the monitoring practices of the firm.

At the conclusion of the inspection an FD 483 was issued to Dr. George M. Grass, Vice-President. Also present for the discussion was John Murphy, Manager of Pre-Clinical Studies, Pharmaceuticals.

At the current time Leland Volker is responsible for the monitoring of clinical studies and reports to J.E. Simpson who in turn reports to Dr. Grass. John Murphy is responsible for monitoring of pre-clinical studies and he also reports to Dr. Simpson. Previously, however, John Murphy monitored university trials and reported to Dr. W.H. Ray, Manager of Scientific Affairs, Pharmaceuticals. Douglas Armstrong, the consultant, was responsible for monitoring of trials by practicing veterinarians in the field and he was doing this strictly on a consultant basis. See Exhibits #1 and #2 for clarification of the Norden chain of command.

ALBENDAZOLE:

Information concerning the Albendazole suspension and paste manufactured and distributed under INAD's 3433 and 3434 was obtained from Dr. W.H. Ray, Manager of Scientific Affairs, Pharmaceuticals, and from Dr. George M. Grass, Vice-President, Pharmaceutical Development Division. Dr. Ray intially stated that they were reluctant to allow inspection concerning the Albendazole product since it was a special case and he felt it did not come under the normal sponsor monitor program. Dr. Ray asked if I wasn't familiar with the Philadelphia District Office inspection of Smith Kline Animal Health Products. He stated that he thought that after that inspection Smith Kline had come to an understanding with the Bureau of Veterinary Medicine that the product should not be covered under the sponsor monitor program. He indicated that he felt that the question was cleared up after that Philadelphia District Office inspection and that we would no longer be asking questions of the firm concerning the Albendazole monitoring. Exhibit #8 to this report is a Smith Kline Animal Health Products internal memo regarding distribution of Albendazole under the INAD. Exhibit #9 is a Smith Kline memo and a letter from Philadelphia District Office concerning the November 15-30, 1983, inspection of Smith Kline. The inspection was terminated for a short time on 2/7/84 so that Dr. Ray could call Smith Kline Animal Health Products and the Bureau of Veterinary Medicine. He continually indicated that he felt that there was no reason for the inspection since the question regarding Albendazole had been cleared up with the Bureau of Veterinary Medicine. After returning to the firm after approximately an hour's absence Dr. Ray asked that I call Dr. Jerry Guest of BVM concerning the inspection. I did so and reported to him that KAN-DO had received a for cause inspection request from

DRB 6/20/84

Dr. Norman Tufts of BVM, Bioresearch Monitoring. I stated that KAN-DO had decided to obtain the necessary facts during the inspection which would be reported to the Bureau of Veterinary Medicine for their review. Dr. Guest stated that as Norden had said it was a special situation; however, he did understand our inspection logic and he had no statements of disagreement. Dr. Ray then provided the information concerning Norden's practices in monitoring Albendazole.

This inspection basically confirmed what Philadelphia District found in that there is very little monitoring taking place concerning Albendazole. The firm's distribution protocol is attached as Exhibit #4 to this report. The firm's basic procedure has been to assure that the product is either shipped to a veterinarian or a supply house with an on-staff veterinarian. Treatment forms are provided to veterinarians with the sale of the product. An example of the current treatment form is attached as Exhibit #3 to this report. The treatment forms are sent directly to Smith Kline Animal Health Products and do not pass through Norden Labs. The firm does audit the branches periodically. Dr. R.M. Grossman, Ph.D., Manager of Pharmaceutical Quality Assurance, is responsible for the branch audits. Attached as Exhibits #5 and #6 are audit reports for Euless, Texas, and Miami, Florida, branches.

I reviewed shipments of Albendazole for the year 1983. Some questionable shipments were found for that period. Most of the questionable shipments concerned shipment to a state not authorized for Albendazole use. Management showed me authorizations for a one-time basis shipment to these states. Each request from an unauthorized state is to be accompanied by an authorization from the Food & Drug Administration. Attached as Exhibit #7 to this report are examples of one-time authorizations for various states. I questioned several other shipments which were made to what appeared to be retail veterinary supply houses. George Grass, Vice-President, stated that as long as there was a veterinarian on the staff they could ship to him. He indicated that this fulfilled their requirements. Attached as Exhibit #23 to this report is a listing of some of the questionable shipments. I also found shipments to wild animal parks in Florida and Oregon. I questioned whether the product was used in the target species at these locations. Management again stated that their only requirement was to ship to a veterinarian.

Attached as Exhibit #10 to this report are all of materials used as information for users of Albendazole. According to Norden management all of these materials have been reviewed and approved by the Food & Drug Administration. Exhibit #11 to this report is labeling for Albendazole suspension and paste. Exhibit #11E is part of the carton for Albendazole 40% paste. According to management this is the old labeling which has been changed after FDA objected to the picture of the cattle on the carton. The picture shown in Exhibit #11E has been deleted.

In summary Norden Laboratories has manufactured and shipped Albendazole paste and suspension. Their only monitoring activities are to assure that distribution is to the name of a veterinarian. Dr. Grossman of Pharmaceutical Quality Assurance is responsible for monitoring activities as far as shipment. Dr. W.H. Ray, Manager of Scientific Affairs, Pharmaceuticals, is responsible for regulatory liaison for the product. All management at Norden stated that any other monitoring activities were unknown to them and would have been carried out at Smith Kline Animal Health Products. They indicated that Helen Birkhead, Manager of Regulatory Affairs and Information Services, was the responsible person at Smith Kline Animal Health Products.

An FD 483, List of Observations, was not issued concerning Albendazole. However, two items were brought to the attention of the firm's management. ① The first was that the SOP's for distribution of the product to the branch warehouses was not signed by a responsible individual. The second item was ② the fact that no complaints were on file at the Norden manufacturing point. Dr. Robert Grossman stated that they had received two complaints regarding the product and these had been forwarded to Smith Kline, Philadelphia, and he could not find copies on file at Norden. Dr. Grossman and Mr. Grass both stated that they felt that both complaints had been forwarded to the Food & Drug Administration. I stated that copies of the complaints should be on file at the manufacturing location.

SPONSOR MONITOR INSPECTION:

John M. Murphy, Manager of Pre-Clinical Studies, Pharmaceuticals, supplied most of the information concerning the clinical studies. Mr. Murphy was previously responsible for portions of clinical studies. He moved to the pre-clinical area in 1983. Clinical investigations are sponsored by Norden Laboratories and conducted at several locations. What the firm calls field trials are conducted by practicing veterinarians in private practice throughout the country. What they call clinical studies are conducted at universities throughout the country in colonies of animals owned by the universities. Norden also has in-house clinical studies in their own animal colony. Mr. Murphy stated that the firm and he in particular had considered the field trials conducted by practicing private veterinarians as the investigations which FDA wanted to be closely monitored. He stated that since animals were owned by the universities those investigations were different and the investigators were more informed because of their positions. The inspection found that generally there was not a large difference between the monitoring activities concerning private veterinarians and university facilities except that regulations were more emphasized for the private veterinarians.

The study chosen for the surveillance portion of this sponsor monitor inspection concerned the product The product is a combination of The product is a chewable tablet for
Attached as Exhibit #14 to this report is the Freedom of Information summary for the product. The summary lists the background data and relevant clinical

investigator data for the product. For purposes of the inspection I focused on studies done by Dr. John McCall at the University of Georgia and Dr. Robert Corwin at the Unviersity of Missouri which were both done on university owned animals. Also I examined records from Dr. Hanover in Illinois, one of the practicing veterinarians involved in the clinical trials. Protocols used in the clinical trials are attached as Exhibits #15 and #16 to this report.

Selection Of And Directions To A Monitor:

As previously outlined John Murphy was responsible for monitoring of clinical trials in university animal colonies and in-house trials. Douglas A. Armstrong, D.V.M., was responsible for monitoring of trials done by practicing veterinarians. Armstrong was a paid consultant at the time he monitored trials. Murphy is a Norden employee. Armstrong's CV is attached as Exhibit #13 to this report. Murphy was responsible for writing protocols and conducting some of the in-house trials. Mr. Murphy's qualifications have been reviewed during previous inspections of Norden Laboratories. There are no written procedures in addition to the protocols which are used for monitoring the clinical investigations. Dr. W.H. Ray, Manager of Scientific Affairs, stated that since there were no actual regulations concerning sponsors and monitor, only proposed regulations, the firm was not attempting to meet any proposed reulations in the monitoring of studies.

511.1(b)(6)

Exhibit #17 to this report is a report filled out by Dr. Douglas Armstrong after a monitoring visit to Dr. John Hanover of Forest Park, Illinois. This form is used for all clinical trials conducted by practicing veterinarians. A form such as this is not filled out for clinical trials in universities. Exhibit #17C is a statement of investigator which is used for these practicing veterinarians. Other portions of Exhibit #17 include a curriculum vitae for Dr. Hanover and protocol changes which were approved by the monitor, Dr. Armstrong. Basically these same types of monitoring activities occurred when studies were done by university personnel. However, the statement of investigator was not completed and there was not as complete documentation concerning visits to the investigator. Mr. Murphy, who monitored the university trials, had a notebook which listed visits to particular investigators and there was also a correspondence file indicating visits to investigators. He did make notations concerning the adequacy of the facilities and other pertinent monitoring data.

TEST ARTICLE ACCOUNTABILITY:

The firm used two different types of accountability procedures during the trials conducted on The latest system included an acknowledgement by the investigator of the exact amount of materials received and an accounting of those materials. There was adequate documentation of shipment dates, quantities, batch numbers, etc. No discrepancies were noted concerning test article accountability.

CONTINUING EVALUATION OF DATA:

Records on hand indicated that there was adequate continuing evaluation of data. John Murphy had complete files concerning correspondence between investigators and the monitor. There was correspondence concerning incomplete case report forms and requests for additional information when incomplete information was received.

A form was used for adverse reaction reporting. Exhibit #18 to this report is one of the completed side effect report forms. In addition to the adverse reaction report form there was a telephone log attached which listed phone conversations concerning the adverse reactions.

Attached as Exhibit #19 to this report is additional information concerning monitoring activities. The exhibit deals with conversations between Dr. Corwin of the University of Missouri, one of the clinical investigators, and John Murphy. were provided to Dr. Corwin by Norden Laboratories. Motility apparently was a problem and Dr. Corwin told Norden that he did not think the were alive as indicated by lack of motility. Exhibit #19 includes a verification letter and a telephone log concerning this. Exhibit #19C is data showing poor recovery of in the University of Missouri study which apparently verifies what Dr. Corwin had said about the motility. It should be noted that although there was a lack of motility the Freedom of Information summary completed by Corwin does indicate that the product was effective against in the University of Missouri study. See Exhibit #14J.

Exhibit #20 to this report is additional information concerning monitoring of the trials and changes to the protocol made by the monitor. Dr. Murphy stated that early on protocol changes were made by simply rewriting the protocol. He stated that later they began to add addendums with protocol changes, leaving the original protocol intact.

Attached as Exhibit #21 to this report is a consent form for the owners of the dogs used in the trial conducted by practicing veterinarians. Note that the consent form states that the drug is safe and effective at the dose to be used in the study. This would appear to contradict current regulations.

Attached as Exhibit #22 to this report is the labeling used for the Filaribits Plus trials.

- OBJECTIONABLE CONDITIONS:

At the conclusion of the inspection an FD 483, List of Observations, was issued to George H. Grass, Vice-President, Pharmaceutical Development Division. The first item listed concerned the failure to document instructions to all clinical investigators concerning the investigational status of the test article and the investigator's obligations. As previously stated this firm differentiates between types of clinical investigators. The clinical investigator in private practice is made aware of all obligations concerning regulations governing clinical trials. However, there is no documentation that university investigators are made aware of these same requirements. Mr. Murphy stated that he was not aware that there was no difference between the types of clinical investigators. He indicated that this had been his perception rather than a company policy.

The consent form used for the clinical investigations represents the product to be safe and effective at the dosage used in the trials. It was pointed out to management that this is contradictory to current regulations which state that the product cannot be promoted as safe and effective. Mr. Grass indicated that the reason for the statement that the product was safe and effective was that they were trying to relay to the animal owner that the product was not going to harm the animal.

DISCUSSION WITH MANAGEMENT:

Discussions held during this inspection are outlined in the report. No additional discussions were held.

EXHIBITS:

Exhibit #1 - Chain of command for Smith Kline Animal Health Products, Veterinary Products Division, Norden Labs.

Exhibit #2 - Chain of command, Pharmaceutical Development Division.

Exhibit #3 - Albendazole treatment form.

Exhibit #4 - Albendazole distribution SOP's.

Exhibit #5 - Branch audit dated 12/13/83, Euless, Texas.

Exhibit #6 - Branch audit dated 12/14/83, Miami, Florida.

Exhibit #7 - Authorizations to ship Albendazole on a one-time basis.

Exhibit #8 - FDA and Smith Kline letters regarding Albendazole usage.

Exhibit #9 - FDA and Smith Kline letters regarding inspection of Smith Kline by PHI-DO.

Exhibit #10 - Albendazole promotional materials.

Exhibit #11 - Albendazole labeling.

Exhibit #12 - CV, Leland J. Volker.

Exhibit #13 - CV, Douglas A. Armstrong.

Exhibit #14 - FOI summary for

Exhibit #15 - Protocol A,

Exhibit #16 - Protocol B,

Exhibit #17 - Monitoring information from Dr. John Hanover, Forest Park, Illinois.

Exhibit #18 - adverse reaction reporting system.

Exhibit #19 - Information concerning viability in Corwin, University of Missouri, study.

Exhibit #20 - Letter from J. Murphy, Norden, to R. Corwin, dated 5/25/82.

Exhibit #21 - Consent form, study.

Exhibit #22 - labeling.

Exhibit #23 - Albendazole shipment.

Jan A. Longenecker

JAL:mlc:2/16/84

Lincoln, Nebraska 68521
2/7-9/84 JAL

Exhibit # 23

Albendazole Shipments

Aid Labs Total 1520 gallons in 1983
Rt. 1 Box 19
1002 NE Park
Okeechobee, Fl. 33472

Stockman Supply Co. Total 190 gallons in 1983
6358 US 27th St. S.
Sebring, Florida 33870

Walco Inc.
Seffner, Florida 8-17-83 60 gallon

Discount Vet Supply 9-20-83 10
RT 1 Box 596 C
Russellville, Ark. 72801

Western Stockmen Supply 3-9-83 4
Box 1027
Nampa, Idaho 83652

Lion Country Safari, Inc
Hwy 80 West 7-19-83 1
W. Palm Beach, Fl. 33416

Safari Game Search Found 5-12-83 2
Box 600 Helwig Rd.
Winston Oregon

Mr. **Weiss**. Now, had the company, to your knowledge, also been relieved of any responsibility for knowingly sending the drug to veterinarians for an improper use?

Dr. **Crawford**. No, they had not.

Mr. **Weiss**. Studies showed that albendazole residues in milk within 1 day after administration of the drug in dairy cattle were more than 1,000 times the "safe" level set by FDA corresponding to a cancer risk of 1 cancer in 1 million population. Was albendazole permitted for use in dairy cattle?

Dr. **Crawford**. No.

Mr. **Weiss**. Nevertheless, Dr. Settepani, notes you wrote in early 1981 stated that the company "is telling folks to write us asking for authorization to use the drug in dairy cattle."

[The notes referred to follow:]

ALBENDAZOLE

Fred - a little background

1. We were supposed to be getting together our letter with all remaining NADA requirements but Dr. Baldwin got tired of waiting for my part and sent out the animal safety + efficacy letter a couple of weeks ago.

2. The investigational use of albendazole has increased significantly. over 29000 head treated in Hawaii alone last month - many thousands in other states.

3 Some annoyances are coming to light. T. McBirkhead at SKF is telling folks to write us asking authorization to use the drug in dairy cattle, goats, and for other parasites such as tape worms, for which we have no efficacy data and no emergency. We (+ Dr. [illegible]) are also bombarded with requests to shorten the 180 day withdrawal period.

4. SKF has asked for a meeting to discuss immediate NADA approval" in view of the new regulatory climate".

5. We found a couple of vets who were giving blanket [illegible] 50, prescriptions to a feed supply outfit that was stocking the albendazole on their shelves.

Joe

Mr. Weiss. Was albendazole, in fact, used in dairy cattle, to your knowledge?

Dr. Settepani. No, to my knowledge it was not. They were encouraging people to write into us to ask for an expansion of the emergency INAD authorization—goat raisers and diarymen and so on. But we never permitted it, as far as I know as part of the emergency authorization.

Mr. Weiss. Let me note for the record that during an August 13, 1984, meeting, Mr. Gary Dykstra of CVM's Office of Surveillance and Compliance told the sponsor that CVM's "biggest concern is the documented case of albendazole being used in dairy cows."

[The FDA memorandum of the August 13, 1984, meeting with the sponsor is in the record.]

Mr. Weiss. Dr. Crawford, do you have any knowledge as to what that concerned?

Dr. Crawford. No, I do not, Mr. Chairman. We can ask Mr. Dykstra to come forward if you would like and convey it either through me or directly. Is that permissible?

Mr. Weiss. Mr. Dykstra, perhaps you ought to do that. Would you?

Do you affirm that the testimony you are about to give is the truth, the whole truth, and nothing but the truth?

Mr. Dykstra. I do.

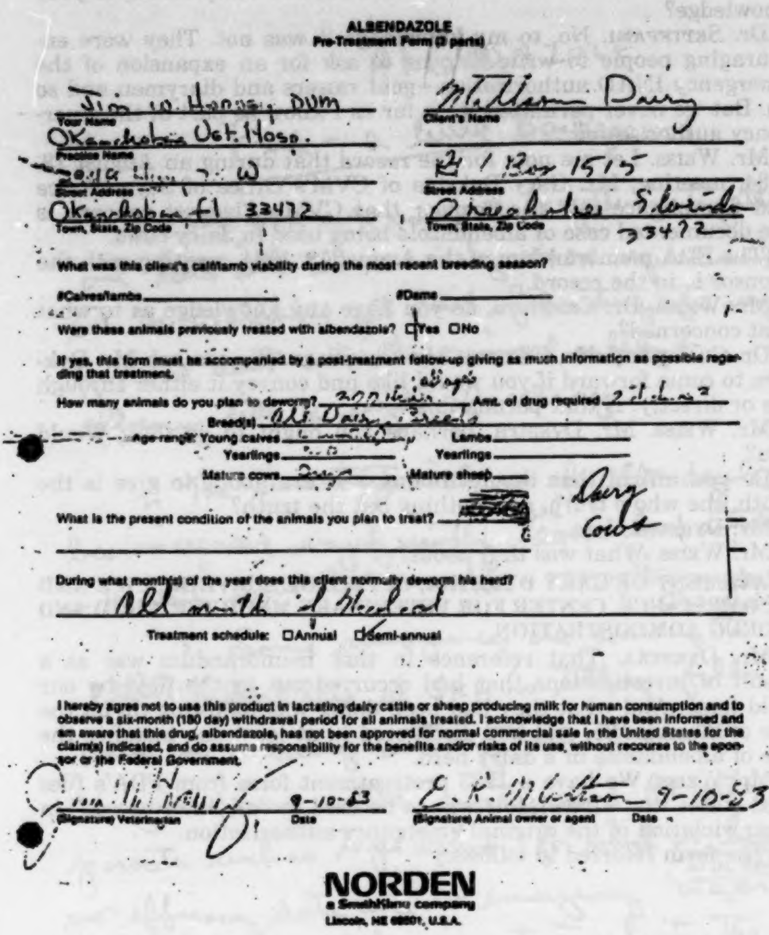
Mr. Weiss. What was that about?

STATEMENT OF GARY DYKSTRA, OFFICE OF SURVEILLANCE AND COMPLIANCE, CENTER FOR VETERINARY MEDICINE, FOOD AND DRUG ADMINISTRATION

Mr. Dykstra. That reference in that memorandum was as a result of investigations that had occurred out in the field by our field force. And what they had been doing was following up on the use of albendazole, and had discovered in at least one instance the use of albendazole in a dairy herd.

Mr. Weiss. We have a 1983 pretreatment form from FDA's files that states that albendazole was to be used in "all dairy breeds" in clear violation of the original emergency authorization.

[The form referred to follows:]



ALBENDAZOLE
Pre-Treatment Form (2 parts)

Your Name: Jim W. Harvey, DVM
Practice Name: Okeechobee Vet. Hosp.
Street Address: 2014 Hwy 7 W
Town, State, Zip Code: Okeechobee fl 33472

Client's Name: McArthur Dairy
Street Address: Rt 1 Box 1515
Town, State, Zip Code: Okeechobee Florida 33472

What was this client's calf/lamb viability during the most recent breeding season?

#Calves/lambs ______ #Dams ______

Were these animals previously treated with albendazole? ☐Yes ☐No

If yes, this form must be accompanied by a post-treatment follow-up giving as much information as possible regarding that treatment.

How many animals do you plan to deworm? 300 heifers all ages Amt. of drug required 2 gallons

Breed(s) All Dairy Breeds

Age range: Young calves [illegible] Lambs ______

Yearlings [illegible] Yearlings ______

Mature cows 2000 Mature sheep ______

What is the present condition of the animals you plan to treat? Dairy Cows

During what month(s) of the year does this client normally deworm his herd?

All months of the year

Treatment schedule: ☐Annual ☑Semi-annual

I hereby agree not to use this product in lactating dairy cattle or sheep producing milk for human consumption and to observe a six-month (180 day) withdrawal period for all animals treated. I acknowledge that I have been informed and am aware that this drug, albendazole, has not been approved for normal commercial sale in the United States for the claim(s) indicated, and do assume responsibility for the benefits and/or risks of its use, without recourse to the sponsor or the Federal Government.

(Signature) Veterinarian 9-10-83 Date

E. R. McArthur 9-10-83
(Signature) Animal owner or agent Date

NORDEN
a SmithKline company
Lincoln, NE 68501, U.S.A.

Mr. **Weiss.** What regulatory action did FDA take upon receiving such treatment forms?

Dr. **Crawford.** You are saying that we approved its use in dairy cattle?

Mr. **Weiss.** No, you received a form which stated that it is to be used for "all dairy breeds." That form was found in your files. I assume that when that kind of clear violation of the original emergency authorization comes to your attention, that the warning bells go off and someone goes out and does something about it. My question is, what?

Dr. **Crawford.** This is a request to use it in dairy breeds, which we would have rejected.

Mr. **Weiss.** This is a pretreatment form which, as we earlier discussed, was sent by a veterinarian receiving albendazole to the sponsor, who forwarded it to FDA. So, it is after-the- fact. It is not a request. It is simply a veterinarian's report to the sponsor as to what he was using or intending to use albendazole for.

Dr. **Crawford.** There is always some question, Mr. Chairman, when we say not for use in lactating dairy cattle, whether or not it can be used in nonlactating dairy cattle. That could have been that.

If someone indicated to us that they used it in lactating dairy cattle, then they would have gotten a visit from FDA.

Mr. **Weiss.** So that if it just says "all dairy breeds" without indicating whether they comprise lactating or nonlactating cattle, you assume that the cattle are nonlactating?

Dr. **Crawford.** We would want to be sure that they were not lactating. Now, such a—perhaps we should see that form, because if it does not tip us off that they are nonlactating, then that should not have been accepted.

Mr. **Weiss.** Well, I wish you would also check your records to see whether there was any effort to determine the extent to which albendazole was used for dairy cattle, and what the agency did as regulatory followup.

Dr. **Crawford.** We will check the record. This appears to be all dairy breeds, and then there is some qualifying languages which says, I believe it reads all months in feedlot on a—can you read that?

I do not know. It could have been nonlactating. We will check.

[The information requested follows:]

Although many references in memoranda and other documents pointed out the possible use of albendazole in lactating dairy cattle, FDA was never able to positively confirm such use through our investigations.

Mr. **Weiss.** In a 1981 submission, the Animal Health Institute (AHI) cited FDA's failure to approve the albendazole new animal drug application as an "example of the animal health drug lag" in the United States.

Dr. Guest, in a May 1981 speech before AHI, you cited the albendazole emergency program as a "gratifying" example of FDA's responsiveness to industry criticism about an animal drug lag.

[Excerpts from Dr. Guest's May 1981 speech before AHI follow:]

Animal Drugs: What's Ahead

Thank you very much for the opportunity to speak at the Animal Health Institute's Annual Meeting. This affords us one more opportunity to communicate and I believe that this is so very important for me and for the Bureau of Veterinary Medicine. I have always enjoyed and valued the interchange appropriate to our respective roles in the animal health field.

This new year -- 1981 -- is an especially proud one for all of us in the Food and Drug Administration. And, on a much broader scale, it is an especially important year for all of us in the United States because we are living in a time and in an environment that allows us to enjoy a quality of life and health that is unique in all the world. This year marks the 75th anniversary of the Food and Drug Administration (FDA) the Nation's pioneer and number one consumer protection Agency.

I will not attempt to retrace and identify the major milestones in FDA's history since 1906, but if one reflects generally on the very rapid advancement of both the human and animal health fields during that time, it is an amazing story, indeed. We have moved from an era of linaments and cathartics to an era of such things as laser surgery, genetic engineering, and ova transplantation. Along with this progress over the 75 years has come peaks and valleys of consumer concern, Congressional interest, and regulatory demands depending on the nature of the issues of the day.

Presented by Dr. Gerald B. Guest, Acting Director, Bureau of Veterinary Medicine, at Animal Health Institute's 41st Annual Meeting May 12-14 1981 in Scottsdale, Arizona.

THE DISCUSSION TO THIS POINT REFLECTS WHAT I BELIEVE ARE THE VERY BROAD OR PHILOSOPHICAL APPROCHES TO ANIMAL DRUG REGULATION THAT I BELIEVE WILL GUIDE THE FDA IN THE NEXT SEVERAL YEARS TO COME.

I WOULD LIKE TO TURN NOW MORE SPECIFICALLY TO A NUMBER OF ISSUES THAT I BELIEVE WILL DOMINATE THE BUREAU OF VETERINARY MEDICINE'S AGENDA FOR AT LEAST THE EARLY YEARS OF THE 80'S.

THERE HAS BEEN GROWING CRITICISM FROM A NUMBER OF AREAS THAT THE FDA'S REQUIREMENTS FOR DRUG APPROVAL AND CONTINUED MARKETING HAVE CONTRIBUTED TO WHAT IS CALLED "DRUG LAG" IN THE UNITED STATES. THE TERM IS MOST OFTEN USED IN THE HUMAN DRUG AREA, BUT I AM BEGINNING TO HEAR THIS COMPLAINT EXPRESSED BY PERSONS IN THE ANIMAL PRODUCTION AND ANIMAL DRUG BUSINESS AS WELL. I WILL NOT ATTEMPT TO DEBATE THE ISSUE OF WHETHER THERE IS OR IS NOT AN ANIMAL DRUG LAG. IF THERE IS THAT PERCEPTION AMONG OUR CONSTITUENTS THEN THAT IS SUFFICIENT TO CAUSE ME CONCERN. I BELIEVE WE CAN ALL AGREE THAT THE CONSUMER IS BETTER SERVED BY HAVING AVAILABLE LARGE NUMBERS AND A WIDE VARITEY OF SAFE AND EFFECTIVE ANIMAL DRUGS. ON THAT SCORE,.I AM SURE WE ARE IN ACCORD. BECAUSE THIS IS A SERIOUS MATTER TO US IN BVM, WE HAVE SEVERAL INITIATIVES UNDERWAY IN THE BUREAU OF VETERINARY MEDICINE WHICH SHOULD HAVE SOME IMPACT ON AT LEAST THE AVAILABILITY OF MINOR USE ANIMAL DRUGS AND NEW DRUG ENTITIES FOR THE TREATMENT OF DISEASE FOR WHICH NO TREATMENT WAS PREVIOUSLY AVAILABLE OR FOR A DRUG THAT CONTRIBUTES TO A SIGNIFICANT BREAKTHROUGH IN DISEASE TREATMENT OR

OR CONTROL. I AM, OR COURSE, REFERRING TO OUR MINOR DRUG USE DOCUMENT, PRECEDURES AND GUIDELINES WHICH WE HOPE TO FINALIZE IN THE NEXT SIX (6) MONTHS. WE ARE PRESENTLY REVIEWING AND REACTING AND RESPONDING TO THE VARIOUS COMMENTS RECEIVED ON THE PROPOSED REGULATION. IN THE SECOND CASE I AM REFERRING TO THE NEWLY INITIATED "FAST TRACK" SYSTEM FOR BREAKTHROUGH ANIMAL DRUGS. WE PRESENTLY HAVE ACCEPTED 13 NEW ANIMAL DRUGS APPLICATIONS (NADA) FOR "FAST TRACK" DESIGNATION. ABOUT ONE-HALF OF THESE ARE FOR FOOD ANIMAL USE.

WE HAVE ALSO INITIATED THE FIRST ORGANIZED USE OF AN EMERGENCY INVESTIGATIONAL NEW ANIMAL DRUG (INAD) IN PROVIDING FOR LIMITED AVAILABILITY OF ALBENDAZOLE FOR THE CONTROL OF LIVER FLUKE INFECTION (FASCIOLA HEPATICA) IN CATTLE AND SHEEP. AS YOU KNOW DISTRIBUTION IS LIMITED TO THOSE AREAS WITH AN ENDEMIC LIVER FLUKE PROBLEM.

I BELIEVE THAT IT IS FAIR TO SAY THAT WE ARE VERY MUCH IN THE EARLY STAGES OF THE LEARNING CURVE IN THESE THREE (3) INITIATIVES, BUT OUR EXPERIENCE TO THIS POINT HAS BEEN VERY GRATIFYING. TIME WILL, OF COURSE, TELL JUST HOW SUCCESSFUL WE WILL BE IN CONTRIBUTING TO SOLUTIONS TO THE ANIMAL DRUG LAG CRITICISM.

IN ADDITION TO THESE INITIATIVES, I BELIEVE IT IS ALSO INCUMBENT UPON US AS REGULATORS TO OUTLINE JUST AS CLEARLY AS POSSIBLE THE STANDARDS FOR DATA NECESSARY TO SHOW ANIMAL DRUG SAFETY AND EFFICACY. I THINK WE ARE REMISS IN OUR RESPONSIBILITIES WHEN WE FAIL TO PROVIDE ADEQUATE, STABLE GUIDANCE TO A

Mr. Weiss. Do you still adhere to that position?

Dr. Guest. Yes, sir. What I was referring to, I think, in that speech was the fact that there are minor-use drugs and orphan drug situations and it is gratifying to me that, with food safety being paramount, when we can be assured that we can use those drugs safely, that we do get them on the market. Yes, sir.

Mr. Weiss. And you hold even after the fact that food safety concerns were of paramount importance throughout the marketing history of albendazole?

Dr. Guest. Yes, sir.

Mr. Weiss. When albendazole was finally recalled, several FDA officials wanted the sponsor to include safety concerns in the recall letter. However, Dr. Crawford, after you met with company officials, all references to safety concerns were excluded from that letter. Why?

Dr. Crawford. You mean the letter that the firm sent out?

Mr. Weiss. Yes.

Dr. Crawford. I am not sure why that would be. Their responsibility essentially was to get it off the shelves, and they were told that we would monitor that, and they had to present a plan for getting it off the shelves, which was to be coordinated by Dr. Bixler's organization. And I am not sure that they were required to list the reason for it in the plan.

Mr. Weiss. Did not Dr. Bixler, for one, want to have safety concerns mentioned in that recall letter?

[A January 1984 memorandum by Dr. Bixler concerning this matter follows:]

MEMORANDUM OF TELEPHONE CONVERSATION

January 14, 1985

Between: Ms. Helen Birkhead
SmithKline Animal Health Products
Philadelphia, PA

and

Dr. William Bixler
Associate Director for Surveillance
and Compliance, CVM

Subject: Albendazole Recall

Ms. Birkhead called to verify that the December 26, 1984, letter from Norden Labs went to 886 veterinarians who had ordered albendazole from Norden Labs during the past 12 months.

Ms. Birkhead reported that those joining her to attend the January 17, 1985, 10:30 a.m. meeting with S&C representatives would be Dr. Grossman, Norden Labs (in charge of the albendazole recall); George Grass, Norden Labs (in charge of research and development); Dr. Cecil Miller, SmithKline (research and development); and Mr. Jordan, SmithKline attorney. I informed Ms. Birkhead that the S&C representatives would be Mr. Dykstra, Mr. Ballitch, Dr. Tufts, Dr. Norcross, Mr. Tsien, and Mr. Lepore.

I informed Ms. Birkhead that we had received a copy of the draft 'Dear Doctor' letter with reference to the albendazole cattle wormer from our Kansas City District Office on January 11 and we were in the process of reviewing/revising prior to giving concurrence. I noted that there was no reference to FDA's safety concerns with the product. Mrs. Birkhead responded by saying that until the independent review panel of pathologists has met and given their opinion that SmithKline will not concur with FDA's conclusions that there is any safety concerns with albendazole. Therefore, SK didn't think that this should be mentioned in the 'Dear Doctor' letter. I informed Ms. Birkhead that CVM does think mention should be made about "recent safety concerns."

William B. Bixler, V.M.D.

cc: HRF-7100 (Mr. Adamson)
HFC-20 (Mr. Celeste)
HFV-2 (Dr. Guest)
HFV-200 (Dr. Bixler)
HFV-230 (Mr. Ballitch)
HFV-234 (Dr. Tufts)
HFV-236 (Mr. Ransdell)
HFV-100 (Dr. Norcross)
HFC-30 (Mr. Brisson)

Dr. **Crawford.** I do not recall. I do not recall that we asked them to do that. Dr. Bixler actually set up the plan with SmithKline for recall, and so he would have been involved in that process.

Mr. **Weiss.** Well, again, given that the carcinogenicity of the drug had been established, would you not think that it would have been appropriate to have the recall letter tell the community at large, which was using this drug, that it was being withdrawn because the product presented safety concerns?

Dr. **Crawford.** As a matter of course in the past withdrawals that we have been involved in, for instance, the DES recalls in 1979, the firms were not required to show what the findings of FDA were. They were required to submit a plan for withdrawal of the product, and they were not required to show what the findings were.

Mr. **Weiss.** Well, how do you feel about that?

Dr. **Crawford.** Well, Mr. Chairman, in many cases we would like to have something done, but we are informed by counsel and also by people within the organization who have experience that we cannot legally require this or that of the firm. It takes place during recalls such as I mentioned with DES and other products. It also takes place in terms of labeling.

Many times we would like a complete toxicology package in the package insert, and we are informed, and sometimes the firms point out to us that we cannot legally require those kinds of things. I am not sure what the legality is of forcing them to say why they were withdrawing the product from the market.

I believe I am correct in saying that the responsibility that we held them to was to get it off the market, and we were concerned that the firm may ask for an administrative hearing prior to taking it off the market, and we believe that our duty to the American people at that point was to suspend its distribution as quickly as possible and not split hairs on how the suspension took place.

Mr. **Weiss.** Are thiabendazole and fenbendazole chemically similar to albendazole?

Dr. **Crawford.** They are related in the same chemical family.

Mr. **Weiss.** In February 1980, thiabendazole's sponsor reported that the drug was associated with an increase in liver tumors, including malignant tumors, in mice. In August 1984, CVM advised the sponsor that it had completed its review of the mouse study.

[FDA's August 1984 letter to the sponsor, and related documentations, follow:]

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville MD 20857

AUG - 6 1984

NADA 13-022

Merck & Company, Inc.
Attn: Mr. R. R. Buck
Assistant Director Regulatory Affairs
P.O. Box 2000
Rahway, New Jersey 07065

Dear Mr. Buck:

We have completed our review of your study entitled "Lifetime Carcinogenic Study in Mice" with thiabendazole which you submitted with a drug experience report of February 29, 1980 for Thibenzole Sheep and Goat Wormer Drench, NADA 13-022. We noted the following findings for liver:

1. An increased incidence of hepatocellular neoplasms in female mice.
2. A complete absence of proliferative liver lesions other than neoplasms.
3. Relatively low incidence of spontaneous liver neoplasms in controls.
4. Very high incidence of hepatic autolysis reported for both male and female mice.

In the light of these findings, we believe that an independent reevaluation of the liver sections is necessary to determine the significance of the liver neoplasms. Therefore, we ask that you submit, for our review, all of the liver sections from the control, low, mid, and high dose groups, both males and females. As an alternative, you may have the slides reviewed by an outside consultant who is acceptable to us.

If you have any questions please do not hesitate to contact us.

Sincerely yours,

David N. Scarr, D.V.M.
Acting Chief, Food Animal Branch
Division of Surveillance
Center for Veterinary Medicine

cc: NADA, DER
HFV-100
HFV-200
HFV-210, SDRF
HFV-214
HFR-2350

MISharar:lph 8/3/84(6)

March 30, 1984

Chief, Diagnostic Pathology Branch
Division of Pathology (HFF-134)

Thiabendazole - Review of the Reported Hepatocellular Lesions in Mice from a Study entitled: "Lifetime Carcinogenic Study in Mice" with Thiabendazole conducted by Merck & Co., Inc. (Study Report dated: January 2, 1980) - Pathology Project No. PR - 50.

Dr. Theodore M. Farber
Director, Toxicology Staff
Center for Veterinary Medicine, HFV-330
Through: Director, Center for Veterinary Medicine, HFV-1
Deputy Director, Center for Veterinary Medicine, HFV-2
Associate Director for Human Food Safety,
Center for Veterinary Medicine, HFV-300
Director, Division of Toxicology,
Center for Veterinary Medicine, HFV-300
Director, Center for Food Safety and Applied Nutrition, HFF-1 TDG
Director, Office of Toxicological Sciences, HFF-100
Director, Division of Pathology, HFF-130 30 Mar 84

References:

1. Memorandum dated April 2, 1981 from Drs. P.R. Sundaresan and J.W. Hauswirth addressed to Dr. R.W. Moch; subject: Lifetime Carcinogenic Laboratory Study with Thiabendazole in Mice"; received in the Division of Pathology on April 7, 1981.

2. Submitted with Ref. # 1 were:

   a. Two (2) Volumes containing data from "Thiabendazole: Lifetime Carcinogenic Study in Mice." (TT # 77-014-0)

   b. A copy of a memorandum from Dr. Jung-Keun Lee, Division of Mathematics (HFF-110) to Dr. P.R. Sundaresan (HFF-154) dated December 24, 1980; subject: Review on Thiabendazole [(NADA-13-022(116)].

   c. A copy of a report from Mr. J.M. Young (Merck Sharp & Dohme) to Dr. R.T. Robertson (Merck Sharp & Dohme) dated September 29, 1980; subject: Thiabendazole: Lifetime Carcinogenic Study in Mice (TT # 77-014-0) Discussion of Results of Supplementary Statistical Analysis; attached to a letter dated October 20, 1980 from J.M. Young to Dr. Jung-Keun Lee.

The Division of Pathology, Center for Food Safety and Applied Nutrition, was requested prior to the transfer of Food Animal Additives

Evaluation Branch from the Center for Food Safety and Applied Nutrition to the Center for Veterinary Medicine (Ref. # 1) to review data dealing with hepatocellular lesions reported in a chronic mouse study with Thiabendazole. Two (2) volumes containing data from the chronic study (Ref. # 2-a) were received in the Division of Pathology, Center for Food Safety and Applied Nutrition, for review of the reported hepatocellular lesions. Also received in the Division for reference and review were copies of two (2) additional reports, one (1) prepared by Dr. Jung-Keun Lee of the Division of Mathematics, Food and Drug Administration (Ref. # 2-b) and the other prepared by Mr. J.M. Young of Merck Sharp & Dohme (Ref. # 2-c). This memorandum contains the Division of Pathology, Center for Food Safety and Applied Nutrition's comments on the reported hepatocellular lesions in the chronic mouse study with Thiabendazole.

A Brief Out-Line of the Study:

The study entitled: Thiabendazole: Lifetime Carcinogenic Study in Mice (TT # 77-014-0), was conducted by Merck Sharp & Dohme Research Laboratories, West Point, PA. A total of six hundred (600) albino mice of the Charles River CD-1 (HaM/ICR) strain were divided into six (6) groups of fifty (50) animals per group per sex. The groups included three untreated control groups and three drug (Thiabendazole) - treated groups. The animals were approximately four (4) weeks old at the start of the experiment. The three (3) dose levels of Thiabendazole initially used were 0.022, 0.066 and 0.200% for male mice and 0.066, 0.200 and 0.533% for female mice. It is stated in the petitioner's submission that the dose levels of Thiabendazole were selected based on the results of a range-finding study (TT # 77-004-0) in an effort to have a dose level which would be the maximally tolerated dose for each sex. However, starting in the seventh (7) week of the treatment, the lowest dose levels of Thiabendazole, i.e., 0.022% in male mice and 0.200% in female mice were both reduced to the 0.006% level. It is indicated that this was done in an effort to have a dose level which would produce "no untoward drug effects." The duration of the feeding period depended upon the number of survivors in a group dropping to ten (10) at which time the animals in that group were terminally sacrificed. Female mice in the high dose (0.533% of the diet) group were sacrificed in the 81st week of the experiment; male mice in the high dose (0.200% of the diet) were sacrificed in the 85th week; male and female mice in the mid dose (0.066% for male mice, 0.200% for female mice) group were sacrificed in the 93rd week and male mice in the low dose (0.006%) group were sacrificed in the 101st week. The petitioner's report states that: "At these times, selected control animals from each of the three control groups were also sacrificed; ... The surviving females in the low dose group and the remaining female controls were sacrificed in the 105th week."

For histopathologic evaluation of tissues/organs, essentially a "full screen" microscopic examination consisting of approximately 26 tissues per animal was made for each of the animals.

Results and Comments:

The incidence of reported hepatocellular neoplasms in male and female mice is summarized in Table 1.

Table 1. Reported Incidence of Hepatocellular Neoplasms

Groups	Hepatocellular Neoplasms		
	Type A	Type B	Type A + Type B
Male mice:	(%)	(%)	(%)
Control I	0/50 (0.0)	2/50 (4.0)	2/50 (4.0)
Control II	1/50 (2.0)	1/50 (2.0)	2/50 (4.0)
Control III	1/50 (2.0)	3/50 (6.0)	4/50 (8.0)
Low Dose (Thiabendazole-0.006%)[1]	0/50 (0.0)	2/50 (4.0)	2/50 (4.0)
Mid Dose (Thiabendazole-0.066%)	0/50 (0.0)	0.50 (0.0)	0/50 (0.0)
High Dose (Thiabendazole-0.200%)	1/49 (2.0)	1/49 (2.0)	2/49 (4.1)
Female Mice:			
Control I	1/48 (2.1)	0/48 (0.0)	1/48 (2.1)
Control II	1/50 (2.0)	0/50 (0.0)	1/50 (2.0)
Control III	1/50 (2.0)	0/50 (0.0)	1/50 (2.0)
Low Dose (Thiabendazole-0.006%)[2]	3/50 (6.0)	0/50 (0.0)	3/50 (6.0)
Mid Dose (Thiabendazole-0.200%)	0/50 (0.0)	1/50 (2.0)	1/50 (2.0)
High Dose (Thiabendazole-0.533%)	1/50 (2.0)	4/50 (8.0)	5/50 (10.0)

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[1] The dose level of Thiabendazole was reduced from the initial dose of 0.022% to 0.006% during treatment week 7.

[2] The dose level of Thiabendazole was reduced from the initial dose of 0.066% to 0.006% during treatment week 7.

The hepatocellular neoplasms as reported in the petitioner's submission are listed as Type 'A' or Type 'B'. The petitioner's report states that: "Dr. Henry Pitot of the McArdle Institute in Madison, Wisconsin, was consulted about the morphologic criteria used in the classification of neoplastic and hyperplastic hepatocellular changes, ... Dr. Pitot stated that he used the terminology of Walker, et. al.[3] and that he placed special importance on the loss of the usual orderly pattern of hepatocytic architecture; i.e., foci in which a relative lack of normal architecture was evident were considered to be Type B nodules regardless of the prominence of other characteristics. His recommendations were followed in the evaluation of liver sections."

No additional comments/explanations as to the morphologic characteristics of the reported hepatocellular lesions, criteria of their classification or to the malignant/non-malignant state of each of the lesions were provided in the petitioner's report. Frith and Ward[4] in their article dealing with a classification system of hepatocellular lesions in mice referred to Type A and Type B lesions as described by Walker et. al. as hepatocellular adenoma (benign neoplasm) and hepatocellular carcinoma (malignant neoplasm), respectively.

In the chronic mouse study with Thiabendazole, the reported incidence of hepatocellular neoplasms, Type A or Type B among the different groups of male mice was similar (Table 1). However, in female mice, the incidence of total hepatocellular neoplasms was reported increased in the high dose group compared to all other groups. Of the hepatocellular neoplasms listed as Type B, four (4) were reported in the high dose group, one (1) in the mid dose group and zero in the low dose and each of the control groups. The incidence of Type A hepatocellular neoplasms in female mice was reported to be one (1) in each of the control groups, three (3) in the low dose group, zero in the mid dose and one (1) in the high dose group. The combined incidence of Type A and Type B hepatocellular neoplasms in female mice in this study was reported to be 5/50, 10.0% in the high dose group vs. 3/148, 2.0% in the three (3) combined control groups.

A statistical evaluation of the hepatocellular lesions made by Dr. Lee (Ref. #2-b) indicated that the incidence of Type 'B' hepatocellular neoplasms showed a significant increase (P=0.004, Fisher's Exact test, 1-tailed) in the female high dose group when compared to the pooled female control groups. Additionally, when types 'A' and 'B' were combined, the incidence also was significantly higher (P=0.029) in the female high dose group when compared to the pooled female control groups.

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[3] Walker, A.I.T., Thorpe, E., and Stevenson, D.E. (1972). The Toxicology of Dieldrin (HEOD). 1. Long-term toxicity studies in mice. Fd Cosmet. Toxicol. 11: 415-432. (Footnote identified by the petitioner as 'a'.)

[4] Journal of Environmental Pathology and Toxicology 3:329-351, 1980.

The denominator figures listed in Table 1 represent the total number of livers examined as listed in the petitioner's report. However, as pointed out in Dr. Lee's memorandum (Ref. # 2-b) and noted also during the review of the data by the Division of Pathology, Center for Food Safety and Applied Nutrition, there was a fairly high number of both male and female mice which reportedly had liver autolysis. According to Dr. Lee's memorandum (Ref. # 2-b), the petitioner reported essentially similar statistical results as that of Dr. Lee's statistical evaluation of the data, although Dr. Lee excluded from the denominator figures any animal with an autolyzed liver. Dr. Lee's memo also reported for female mice that: "It was concluded that the data of type 'B' hepatocellular neoplasms showed a significant positive trend ($P < 0.001$) for females as the dose level increased."

A review of the individual animal data indicates, based on the mortality record of animals, that there was an earlier occurrence of hepatocellular neoplasia in the high dose group of female mice compared to the control group of female mice. Treated female mice were sacrificed in the 81st week of the experiment. The study was deficient in that different groups were sacrificed at different times which does not allow for an appropriate comparison of the data among the groups. Nevertheless, as noted from Dr. Lee's memorandum: "In females the first type 'B' hepatocellular tumor was observed at 532 days in the high dose group, at which time 15 mice (30%) of the high dose group were at risk. If animals lived longer, more tumors might be observed in the female high dose group, because 3 of 4 type 'B' tumors were found at sacrifice (i.e., 564 days)."

In its review of the data, the Division of Pathology considers it somewhat unusual that not a single animal in the study was listed as having any proliferative lesion(s) of the hepatocytes such as foci or areas of cellular alteration.

It was stated in the petitioner's summary of the reported data that: "The mean liver weights were greater in males and females given the highest concentrations and in females given the middle concentration compared to the controls". There was no data/information provided in the petitioner's submission as to whether or not any gross findings in the liver were noted at the time of necropsy.

Hepatocellular neoplasms may occur spontaneously in mice. Based on the reported spontaneous incidence of hepatocellular tumors in most strains of mice, male mice are generally more susceptible than female mice. In consideration that the hepatocellular neoplasms in the Thiabendazole study might be spontaneous, a somewhat unusual finding is noted in that the increased incidence of these tumors was reported in female mice. The petitioner has provided (Ref. # 2-c) background historical information from two studies done at their laboratory. The data are provided as total hepatocellular neoplasms and no information is provided as to the occurrence and distribution of benign and malignant lesions. The unanswered questions regarding the data submitted by the petitioner as historical control data render the data of limited value insofar as it being used in a valid comparison with the data from the Thiabendazole study.

The petitioner's pathology report[5] states that: "The number of hepatocellular neoplasms was similar in drug - treated and control groups, although the incidence of Type 'B' hepatocellular neoplasms was slightly greater in females given the highest concentration. The latter difference was not considered biologically significant, however, since Type 'A' and Type 'B' lesions are considered not qualitatively different and the incidence of hepatocellular neoplasms was similar in each group when males and females were combined."

Since the petitioner's report does not elaborate on the qualitative/morphologic characteristics of hepatocellular lesions listed in this study, the Division of Pathology has no basis to accept the petitioner's rationale that "... although the incidence of Type 'B' hepatocellular neoplasms was slightly greater in females given the highest concentration. The latter difference was not considered biologically significant, ..." More definitive explanations/comments by the petitioner may assist in resolving questions regarding the qualitative nature and the circumstances of occurrence of the increased incidence of hepatocellular neoplams in female mice. Likewise an independent re-evaluation of the liver microslides may be considered to be desirable in any attempt to ascertain the qualitative and morphologic characteristes of the reported hepatocellular neoplasms.

Since there was no apparent similar response to the occurrence of hepatocellular tumors in males and females, the data of hepatocellular neoplasms in males and females should be evaluated separately and not be combined as suggested in the petitioners' pathology summary report.

Conclusions:

1. Although the numerical incidence (numbers) of hepatocellular neoplasms occurring in the Thiabendazole study is not very striking, the reported data in female mice suggest a possible treatment-related effect in the occurrence of these lesions. This suggestion is based on:
   - a) an apparent earlier occurrence of hepatocellular tumors in the high dose female mice vs the control group mice;
   - b) a majority of the hepatocellular neoplasms (4 out of 5) in the female high dose group were reported to be Type "B", i.e., malignant neoplasms;
   - c) a statistically significant increase of both Type "B" and the combined Type "A" and Type "B" hepatocellular neoplasms in

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[5] Page 213 of the petitioner's submission.

the high dose female group vs similar entities in the three combined control groups.

2. **A somewhat unusual finding in this study is the fact that the increased incidence of hepatocellular tumors was noted in female mice. Based on the reported spontaneous incidence of hepatocellular tumors in most strains of mice, male mice are generally more susceptible than female mice.**
3. **The petitioner's report does not elaborate on the qualitative/morphologic characteristics of hepatocellular lesions reported in this study. Additional explanation/comment may be sought from the petitioner to clarify the qualitative nature and the circumstances of the occurrence of these lesions in female mice.**
4. **An independent re-evaluation of the liver microslides may be considered desirable to ascertain the qualitative and morphologic characteristics of the hepatocellular lesions.**

Prem N. Dua, D.V.M., Ph.D.

cc:
HFF-100 (Dr. Flamm)
Central Files

PNDua:dlm:HFF-134
Doc#281:Disk#30

Mr. Weiss. Why did it take FDA more than 4 years to conclude that the sponsor had reported increases in liver tumors?

Dr. Crawford. I am not familiar with that particular analysis. Perhaps Dr. Settepani is. If not, we may have to submit it.

[The information requested follows:]

The Bureau of Foods' Division of Pathology had a considerable backlog at the time (1981). In addition to various direct and indirect food additives they were reviewing studies on at least two other animal drugs which were of higher priority—that is drugs that were not already approved as thiabendazole. Also during this time the human food safety function was transferred from the Bureau of Foods to the Center for Veterinary Medicine resulting in some confusion as to whose responsibility it was to review this submission as well as others. Bureau of Foods agreed to do it in a low priority status.

Mr. Weiss. Dr. Settepani?

Dr. Settepani. I do not know the reason for the delay.

Mr. Weiss. Would you agree that almost a 4½-year delay is really unwarranted?

Dr. Crawford. Mr. Chairman, I assume they were analyzing the relevant literature. It seems a long time to me, and I agree with you. Many times what will happen, if I can digress for just a few seconds, you see, the sponsoring firm is required to report to CVM any adverse effects, any adverse reports in the literature, anything that should be brought to our attention about the potential continued approvability of the compound.

Now, having done that, in many cases the relevant scientific literature will have offsetting reports. Some reports will say the product is carcinogenic; others say it is safe. It is incumbent upon FDA, I think, to assess the scientific literature to see what it reveals in its totality, and then make a decision.

It is unusual for that analysis to take 4 years, but I think you will agree that we cannot be in the position of acting on independent reports that may not reflect the current state of knowledge.

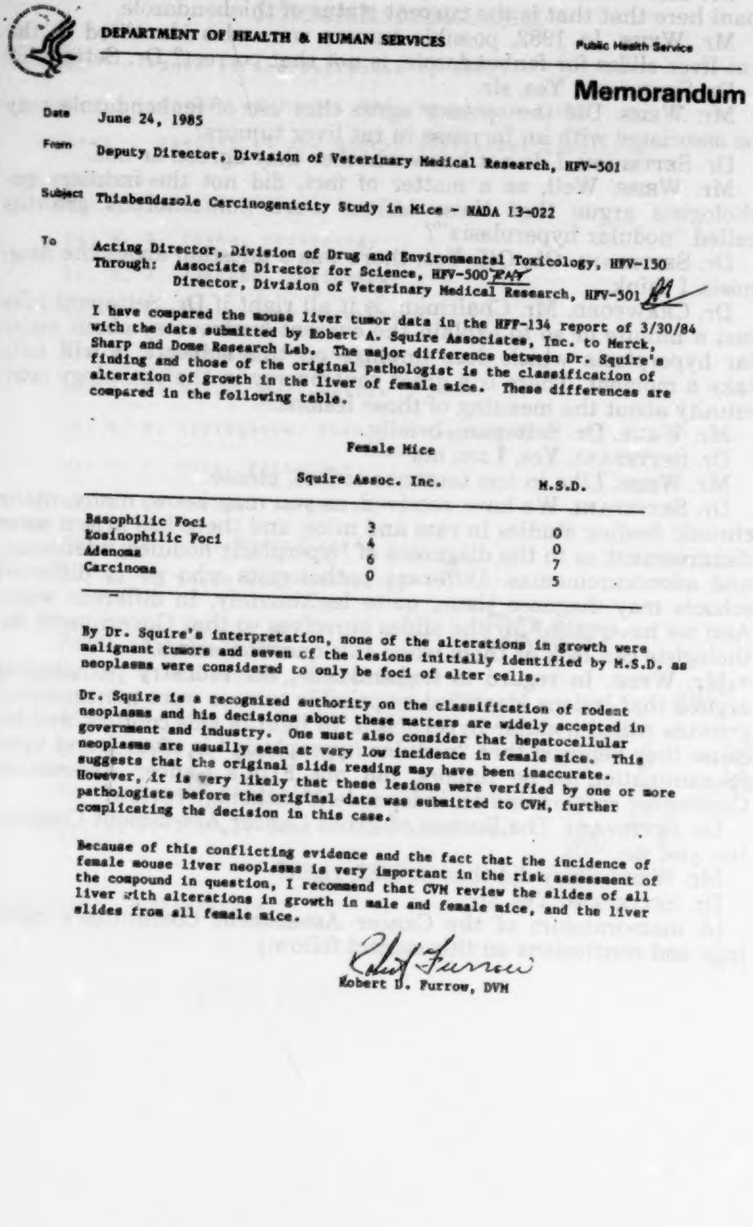
Mr. Weiss. This, however, involves the sponsor's reporting that to you in the first instance.

Recently, another pathologist hired by the sponsor concluded that none of the liver tumors was malignant and previously diagnosed benign tumors weren't even tumors at all. In light of this conflicting evidence, what did CVM's pathologists recommend, if you know?

Dr. **Crawford**. Well, I am sure they analyzed the reports. And this, I think, strengthens what I just said, and that is that we cannot act precipitously when we get such a report as that. I think it is incumbent upon us to review all the relevant literature, and in the face of a damning study on an approved compound, more and more the relevant scientific association such as the American College of Pathology are recommending data audits; that is, independent reviews of the slides. That may have been done in that case. I am not sure.

Mr. **Weiss**. Our records indicate that on June 24, 1985, CVM's pathologist recommended that CVM review all of the liver slides itself.

[The pathologist's June 24, 1985, memorandum on this subject follows:]



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Date June 24, 1985

From Deputy Director, Division of Veterinary Medical Research, HFV-501

Subject Thiabendazole Carcinogenicity Study in Mice - NADA 13-022

To Acting Director, Division of Drug and Environmental Toxicology, HFV-130
Through: Associate Director for Science, HFV-500
Director, Division of Veterinary Medical Research, HFV-501

I have compared the mouse liver tumor data in the HFF-134 report of 3/30/84 with the data submitted by Robert A. Squire Associates, Inc. to Merck, Sharp and Dome Research Lab. The major difference between Dr. Squire's finding and those of the original pathologist is the classification of alteration of growth in the liver of female mice. These differences are compared in the following table.

Female Mice

	Squire Assoc. Inc.	M.S.D.
Basophilic Foci	3	0
Eosinophilic Foci	4	0
Adenoma	6	7
Carcinoma	0	5

By Dr. Squire's interpretation, none of the alterations in growth were malignant tumors and seven of the lesions initially identified by M.S.D. as neoplasms were considered to only be foci of alter cells.

Dr. Squire is a recognized authority on the classification of rodent neoplasms and his decisions about these matters are widely accepted in government and industry. One must also consider that hepatocellular neoplasms are usually seen at very low incidence in female mice. This suggests that the original slide reading may have been inaccurate. However, it is very likely that these lesions were verified by one or more pathologists before the original data was submitted to CVM, further complicating the decision in this case.

Because of this conflicting evidence and the fact that the incidence of female mouse liver neoplasms is very important in the risk assessment of the compound in question, I recommend that CVM review the slides of all liver with alterations in growth in male and female mice, and the liver slides from all female mice.

Robert Furrow

Robert D. Furrow, DVM

Dr. **Crawford**. Yes. I have just been handed a note by Dr. Settepani here that that is the current status of thiabendazole.

Mr. **Weiss**. In 1982, possible tumors were also identified in the rat liver slides for fenbendazole; is not that correct? Dr. Settepani?

Dr. **Settepani**. Yes, sir.

Mr. **Weiss**. Did the sponsor agree that use of fenbendazole may be associated with an increase in rat liver tumors?

Dr. **Settepani**. I do not know whether they agreed or not.

Mr. **Weiss**. Well, as a matter of fact, did not the industry pathologists argue that these lesions were nontumorous growths called "nodular hyperplasia"?

Dr. **Settepani**. Oh, OK. Yes, there was a question about the diagnosis, I think.

Dr. **Crawford**. Mr. Chairman, is it all right if Dr. Settepani take just a minute or so to explain the current controversy about nodular hyperplasia which does impinge on this subject? It will only take a moment. There is a great controversy in the pathology community about the meaning of those lesions.

Mr. **Weiss**. Dr. Settepani, briefly.

Dr. **Settepani**. Yes, I am not——

Mr. **Weiss**. Like in one sentence or less, please.

Dr. **Settepani**. We have received, as you may know, many, many chronic feeding studies in rats and mice, and there has arisen some disagreement as to the diagnoses of hyperplasic nodules, adenomas, and adenocarcinomas. Different pathologists who go to different schools may diagnose them, quite legitimately, in different ways. And we have asked for the slides ourselves so that Government pathologists can look at them when this question arises.

Mr. **Weiss**. In regard to fenbendazole, the industry pathologists argued that lesions identified as possible tumors were nontumorous growths called nodular hyperplasia. In light of this conflict, and because they believed that "nodular hyperplasia" is often found upon reexamination to be tumors, did not FDA's Cancer Assessment Committee recommend an independent pathology review?

Dr. **Settepani**. The Bureau of Foods Cancer Assessment Committee, yes, sir.

Mr. **Weiss**. They did that in 1982, right?

Dr. **Settepani**. Yes, sir.

[A memorandum of the Cancer Assessment Committee's meetings and conclusions on this subject follow:]

MEMORANDUM OF CONFERENCES

Dates: June 22 and September 9, 1982

Place: Bureau of Foods, FDA, Washington, D.C.

Purpose: Meeting of the Cancer Assessment Committee

Participants:

CAC Members

Dr. W. G. Flamm, Toxicology

Dr. B. A. Jackson, Toxicology

Dr. M. A. Weinberger, Pathology

Dr. H. Blumenthal, Toxicology

Mr. R. N. Brown, Mathematics

Dr. R. C. Livingston, Chemistry and Physics

Dr. R. W. Moch, Pathology

Dr. T. M. Farber, Toxicology

Dr. C. S. Lin, Toxicology

Dr. R. J. Lorentzen, Toxicology

Other Participants

Dr. J. W. Hauswirth, Toxicology

Mr. D. I. Ruggles, Mathematics

Dr. R. Gryder, Toxicology

Dr. S. Green, Toxicology

Dr. S. F. Andres, Food Animal Additives

DRAFT

going around for sign off

Subject: Fenbendazole

The Committee was requested to evaluate a chronic rat feeding study performed on the animal drug, Fenbendazole, with particular attention to the results reported for the liver. The Charles River (Sprague-Dawley)-derived rats were administered the drug at doses up to 135 mg/kg/b.w./day in the diet for about 28 months after an in utero exposure phase. The results of the study indicated a dose-related toxic effect on the liver in both sexes, including the production of lesions designated focal and nodular hyperplasia by the histopathological evaluation. The sponsor of Fenbendazole arranged for an independent pathology review of the liver microslides. The results of this review also indicated that the drug had a toxic effect on the liver, including the induction of lesions designated as focal and nodular hyperplasia. There were more diagnoses of hepatocellular adenoma and carcinoma in this latter review and most of these occurred in the dosed groups. However, the numbers were not large and did not appear to reflect a significant treatment related response. Nevertheless, the Committee was uneasy with the rather substantial differences in diagnoses and nomenclature used by each pathology analysis. Descriptions obtained by the sponsor, from each pathologist, of the morphological nature of the individual categories of proliferative lesions diagnosed by each of them failed to resolve for the Committee the discrepancies in their diagnoses or provide a basis to infer the real nature of the lesions. In the interest of saving the time and effort of the sponsor, the Committee and our pathology resources, we recommended that a conference call be arranged between a Committee member from the Division of Pathology, Dr. Weinberger, and the study's two contract pathologists, along with a few other appropriate scientists from the Bureau and whomever else the sponsor desired. The principal outcome of this conference was an agreement by the sponsor and their contract pathologists to attempt to reach a consensus diagnosis on those hepatocellular proliferative lesions diagnosed by either of them as nodular hyperplasia, adenoma or carcinoma, and to designate which, if any, of these would, in their judgment, be consistent with the criteria of the terminology "neoplastic nodule" used by other pathologists. The hope was that this might be sufficient to resolve the liver issue in Fenbendazole treated rats.

The results of the consensus diagnoses subsequently submitted were examined by the Committee. As with the previous pathology reviews, this review also indicated that there is an effect of Fenbendazole on hepatocytes, particularly noticeable in female rats. This effect was expressed as a dose-related increase in "nodular hyperplasia." The incidences of neoplasms, including "neoplastic nodules," were increased in the high dosage groups. However, as with one of the earlier reviews, the increases were not large enough to be considered significant.

DRAFT

The resolution of the present situation hinges on understanding the biological meaning of the term "nodular hyperplasia." From the diagnoses rendered, there is an apparent proliferative effect on the hepatocytes associated with treatment. Many scientists interpret this to reflect a neoplastic process or progression in rodent liver. The Committee has traditionally taken the position that an increased incidence of altered foci of hepatocytes alone was not sufficient evidence of a neoplastic effect, but that it could provide support for an apparent neoplastic effect described by an increase in the incidence of neoplastic nodules, adenomas or carcinomas. The occurrence of many lesions diagnosed as "nodular hyperplasia" leaves the Division of Pathology and the Committee in doubt about the true biological and morphological nature of this lesion. For rats, this diagnostic terminology "nodular hyperplasia" has been used in past literature to describe both benign and malignant lesions of hepatocytes. Microslide reviews in the past have revealed that lesions given this terminology can be either neoplastic or non-neoplastic. As such, without a thorough review, the Committee concludes it cannot determine whether the increase in incidence of "nodular hyperplasia" associated with the administration of Fenbendazole represents a neoplastic or non-neoplastic event.

In summary, an independent pathology review of the initial diagnoses of liver lesions in the Fenbendazole study performed in rats, and a subsequent attempt to resolve the differences in diagnoses rendered, both indicate that there is an increased incidence of proliferative lesions of the hepatocytes associated with the administration of Fenbendaole. However, for reasons described above, a thorough pathology review of the liver microslidee is needed to determine whether the effect observed represents a neoplastic or non-neoplastic event.

Ronald J. Lorentzen, Ph.D.
Executive Secretary

DRAFT

cc:
HFF-1
HFF-2
HFF-152 (Edwards)
HFF-159 (Bolger)
All Attendees

RJLorentzen:gz 9/20/82 0444A .
Final - 10/27/82

Mr. **Weiss**. Did CVM arrange for an independent review, as recommended by the Cancer Assessment Committee?

Dr. **Settepani**. No, sir. What happened in that case was the Center for Veterinary Medicine's pathologist, as I understand it, knew the two pathologists that had reviewed the slides for the sponsor. He called them on the phone and resolved the diagnosing differences or questions with them, and he was convinced that they were diagnosing the tumors the same way that an FDA pathologist would, and he recommended that we would not need to look at the slides.

Mr. **Weiss**. So, CVM's pathologist rejected the unanimous recommendation of the Cancer Assessment Committee and relied totally on the word of industry scientists, because he felt that they were well-credentialed or what have you; he could vouch for their scientific expertise.

[The CVM's pathologist's December 22, 1982, memorandum concluding that an independent review of the fenbendazole slides is unnecessary, follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Date December 22, 1982

From Research Veterinary Medical Officer (Pathology), DVMR, HFV-540

Subject NADA 128-620 Fenbendazole Suspension 10%, Anthelmintic for Cattle

To Dr. T. M. Farber, Chairman, Cancer Assessment Committee, HFV-330

I have reviewed the correspondence from the American Hoechst Corporation dated June 15, August 10, and December 1, 1982 and the memorandum of conferences of the Cancer Assessment Committee (CAC) of June 22 and September 9, 1982. I discussed the problem of terminology clarification with members of the CAC and with Hoechst's scientists and consulting pathologists.

The problem, as stated by the CAC, involves the interpretation of the term "nodular hyperplasia" used to describe altered areas of growth and morphology in livers from the chronic rat study.

The sponsors contract pathologist separately and in a consensus report did not identify a significant number of neoplasms (adenomas, carcinomas) or "neoplastic nodules" in the rat livers. Both of the contract pathologists are Diplomates of the American College of Veterinary Pathology with extensive experience in rodent pathology and toxicologic pathology. These pathologists verbally and in writing have asserted that "nodular hyperplasis" in the rat livers from this study are not neoplasms. In difference with the conclusion of the Bureau of Foods CAC, I do not believe it is necessary to review the liver microslides to conclude that the "nodular hyperplasia" described in the consensus report are focal areas of altered growth and not are neoplasms.

In summary, there is a dose related alteration in growth of hepatocytes which is more pronounced in females in the two year rat study. These alterations in growth and morphology do not progress to neoplasia (adenoma, carcinoma). The incidence of hepatic neoplasms is within the range expected for the strain of rat used in this study. Therefore, I conclude that there is insufficient evidence in the liver lesions in the two year rat study to show a carcinogenic effect for Fenbendazole.

Robert Furrow

Robert D. Furrow, D.V.M.
Diplomate ACVP

Dr. **Settepani**. Well, I do not think he rejected the unanimous conclusion. I think he thought that he had resolved the issue.

Mr. **Weiss**. Well, the fact is that the Bureau of Foods' Cancer Assessment Committee made that recommendation for an independent review, right?

Dr. **Settepani**. Yes, sir. They had spoken to the——

Dr. **Crawford**. Mr. Chairman, I think what they recommended was is that there be a review, not that they were convinced that it was carcinogenic. And essentially what the pathologist at CVM did was to determine whether or not, in fact, he believed there should be a review.

Mr. **Weiss**. Well, you were just telling us that the way to deal with the scientific controversy that has arisen concerning these types of lesions is to have an independent review. And what I gather from these two cases, one dealing with fenbendazole, and the other dealing with thiabendazole is that where the finding is that tumors have developed, then you review the slides. But where the finding, according to industry, is that the animals developed nodular hyperplasia rather than tumors, and the recommendation is that you review the slides, you do not review them. Now, it seems to me that this is less than the even-handed scientific independent review that you suggested takes place. It seems to me that it is a heads, I win—tails, you lose kind of situation.

Dr. **Crawford**. Well, it is a close call, Mr. Chairman, because the nodular hyperplasia is by definition not a cancer. The question is whether or not it can revert to a cancerous state or not. And there have been differing opinions down through recent history about the significance of nodular hyperplasia, and there continues to be.

Mr. **Weiss**. Did not Government pathologists conclude in 1981 that avoparcin induced tumors in rat livers?

Dr. **Crawford**. Mr. Chairman, avoparcin, if I may say, is a product under review at the present time. It has not been approved for the market. We would prefer not discussing data with respect to it.

Mr. **Weiss**. Well, without discussing data, you will tell me whether, in fact, it is appropriate to respond. Did not industry consultants characterize tumors in avoparcin as nodular hyperplasia?

Dr. **Crawford**. If I may ask counsel whether or not we can respond. That drug is not approved.

Mr. **Weiss**. It is still under investigation.

Dr. **Crawford**. Still under investigation.

Mr. **Weiss**. OK, forget it.

Let us turn to the use of gentian violet in poultry feed. Is this use of gentian violet generally recognized as safe or GRAS?

Dr. **Crawford**. Gentian violet is a product that FDA has attempted over the past recent years to remove from the marketplace because of suspected mutagenicity and possible carcinogenicity. As you may know, FDA took vigorous action in 1979, 1980, and 1981 to accomplish that. We were overturned in the court. The court held in 1981 that a certain level of gentian violet was safe. In fact, generally recognized as safe.

Subsequent to that trial in which we lost, we had initiated a long-term study, not subsequent to but actually before the trial, we had initiated a long-term study of the effects of gentian violet which is now being completed at the National Center for Toxicological Research in Arkansas. And we will take the appropriate action when that research is completed.

Mr. **Weiss**. How many times have other courts upheld FDA regulatory actions on the grounds that gentian violet was not generally recognized as safe and may not legally be added to poultry feed?

Dr. **Crawford**. Until the time of the 1981 decision, the court had generally upheld our actions.

Mr. **Weiss**. That Georgia court did not overrule those earlier decisions. It was not a higher level court, was it?

Dr. **Crawford**. It was the Fifth Circuit Court, I believe.

Mr. **Weiss**. But it was a trial court level, right?

Dr. **Crawford**. It was a trial court level, yes.

Mr. **Weiss**. And that was the first time in which the ruling or the finding went against FDA. Is that correct?

Dr. **Crawford**. I think we had had some setbacks in the court, but generally we had been supported, yes.

Mr. **Weiss**. So you would not have been forced, on the basis of that one decision, to follow that decision, as distinguished from the other court decisions which went in your favor and were made at least at the same level. Is that correct?

Dr. **Crawford**. Actually the most recent support of us prior to 1981 had occurred in that same Fifth Circuit Court. And, so, in effect, the strongest legal opinion we were depending upon had, in fact, been overturned in the same court under the same judge.

Mr. **Weiss**. That is—again if I can give you legal counsel——

Dr. **Crawford**. Please.

Mr. **Weiss**. That is not the way it works.

Dr. **Crawford**. Yes, OK.

Mr. **Weiss**. If courts at the same jurisdictional level hand down different decisions, no one decision is binding until at least an appellate court finds one way or the other. Then it seems to me you have higher authority. A 1980 GAO report stated that in "9 of 10 cases where FDA regulatory actions were challenged in court, the courts agreed with FDA's position on the use of gentian violet for veterinary purposes." So, the Georgia case, in fact, could be construed to be the aberration, rather than the ruling decision.

Dr. **Crawford**. Mr. Chairman, perhaps we would let counsel speak on this matter.

Mr. **Weiss**. Please. Mr. Drozen.

Mr. **Drozen**. I believe—it is my recollection, Mr. Chairman, that this was the first and only decision that Dr. Crawford is referring to, the first and only written opinion of a district court, and granted it was a trial court level, there is no appellate decision that dealt with the issue of the general recognition of the safety of gentian violet.

I would believe that what the GAO report is referring to is other cases that we brought successfully and that essentially really were not challenged. They eventually resulted in decrees in favor of the Government, but in terms of the legal effect of those decrees, they are virtually meaningless in view of the district court's written opinion on gentian violet.

Mr. **Weiss**. Are you saying that FDA's regulatory action in regard to gentian violet had never been challenged in courts previously?

Mr. **Drozen**. I do not believe—I do not recall a formal district court opinion prior to the opinion in 1980 or 1981.

Mr. **Weiss**. Well, a judicial opinion aside, what about a legal or court challenge?

Mr. **Drozen**. No, I believe that when I am saying court challenge, the cases may have been contested up to a certain step.

Mr. **Weiss**. Right.

Mr. **Drozen**. I do not disagree with that. I do not have any specific personal recollection of that. What I am saying is that those cases did not, to the best of my recollection, result in a formal written decision on the issue of the general recognition of safety of gentian violet. They may have resulted in consent decrees of condemnation for the product that was seized. But the legal force of those consent decrees is minimal in comparison to a written decision which we have from a court in the fifth circuit. That is the best of my recollection, Mr. Chairman.

Mr. **Weiss**. Well, you are saying that a written opinion from the court of the same level of jurisdiction overrules the prior cases in which the agency succeeded at the same judicial level?

Mr. **Drozen**. I do not mean to quarrel with you over semantics, Mr. Chairman.

Mr. **Weiss**. OK.

Mr. **Drozen**. And I am sure that you are aware of the difficulty that may be posed once we have a written, a written decision that we now have to deal with that can be cited as authority in effect against us in subsequent cases.

The cases that went in our favor were decisions that in effect were settled. They were in our favor, but they were settled in our favor. There is very little authority—we cannot very easily use them as persuasive authority in subsequent lawsuits when we have a specific court decision in writing by a district court judge against us.

Mr. **Weiss**. Although we have some other questions, we have just received the message for another vote. Rather than pursue them at this point, we will submit our additional questions to you in writing, and will appreciate your responding as expeditiously as possible. We will hold the hearing record open for you to be able to do that for us.

[The subcommittee's September 30, 1985, letter to FDA Commissioner Frank E. Young, enclosing several additional questions for the record, and FDA's November 21, 1985, response, follow:]

TED WEISS, NEW YORK, CHAIRMAN
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NINETY-NINTH CONGRESS
Congress of the United States
House of Representatives
INTERGOVERNMENTAL RELATIONS AND
HUMAN RESOURCES SUBCOMMITTEE
OF THE
COMMITTEE ON GOVERNMENT OPERATIONS
RAYBURN HOUSE OFFICE BUILDING, ROOM B-372
WASHINGTON, DC 20515
(202) [illegible]

September 30, 1985

Frank E. Young, M.D., Ph.D.
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Young:

In order to complete the record of the subcommittee's review of the regulation of new animal drugs, we would appreciate receiving responses to the following questions by Friday, October 18, 1985.

If there are any questions concerning this request, please have your staff contact Daniel Sigelman in the subcommittee office.

Thank you for your cooperation in this matter.

Sincerely,

TED WEISS
Chairman

Attachment

QUESTIONS FOR THE RECORD ON FDA's REGULATION OF ANIMAL DRUGS

1. Since 1983, how many unapproved new animal drugs has CVM directed to be removed from the market? During the same period, how many unapproved new animal drugs have been introduced to the marketplace?

2. Dr. Crawford testified that, in response to the widespread marketing of unapproved new animal drugs, CVM initiated an extra-label use program designed to ensure a veterinarian/client/patient relationship in the administration of prescription drugs. However, the extra-label use program only covers drugs that have already been approved for at least one use. How does this program address the problem presented by the marketing of thousands of new animal drugs not covered by approved NADAs?

3. How many FTEs, broken down by field and headquarters, are currently allocated to the objective of combatting the marketing of unapproved new animal drugs?

4. What does FDA estimate to be the cost of bringing CVM into compliance with drug listing and registration requirements?

5. On September 9, 1985, Mr. Clifford Shane advised the subcommittee staff that in both FY '84 and FY '85 FDA allocated 1.3 person-years to combatting the illegal sale of veterinary prescription drugs throughout the United States. Although his region was allocated .27 and .30 person-years for this objective in FY '84 and FY '85 respectively, his region is currently using 1 person-year for this purpose. On August 8, 1985, Dr. Beaulieu confirmed that the field has "overburned" the resources allocated to this objective. Have FDA and the Department requested additional resources to meet this problem?

6. Please supply, for fiscal years 1983-86, copies of all CVM submissions requesting additional resources. Also please indicate whether and, to what extent, CVM was awarded any resource increases it had requested.

7. In a January 14, 1980, memorandum on agency recommendations for a cyclic review of animal drugs, Dr. Robert J. Scheuplein, then Director, Food Animal Additives Staff, wrote that "[m]ost marketed animal drugs have been approved on the basis of safety evaluations currently considered indequate" and that "it is very likely that if all . . . approved drugs were re-evaluated in the light of current science and policy, that several couldn't meet the 'shown to be safe' standard and that many more would require revised tolerances." In a July 9, 1980, memorandum to the Commissioner, Dr. Crawford wrote that he thought it was neither economically nor politically feasible to ask industry to produce additional data to support the safety of their already approved drugs. Cyclic review of animal drugs, therefore, was never undertaken. Is it FDA's position that re-evaluations of whether animal drugs still meet the safety requirements of law should be based on economic or political rather than safety grounds?

8. Cyclic review of animal drugs was intended to include a re-evaluation of whether existing regulatory methods for detecting animal drug residues met current guidelines, since most of the animal drugs for which adequate methods are unavailable were approved many years ago. Inasmuch as development of practicable methods for detecting animal drug residues is a condition of NADA approval, Dr. Crawford testified that FDA "will have to take action to take . . . off the market" any drug for which adequate detection methods cannot be developed. What timetable has FDA established to ensure that approved new animal drugs in use are supported by adequate methods for detecting their residues and those of their metabolites in milk and edible animal tissues? Has FDA advised sponsors of the deadlines they must meet for developing such methods?

9. Has FDA ever defined for sponsors what constitutes the required specificity for a regulatory method?

10. Have there been any additional updates of the 1972 Johnson memorandum since 1979? If so, please provide copies of all such updates.

11. The Committee to Analyze Presently Approved Detection Methods of Food Animal Feed Additives (the Andres Committee) recommended in its December 28, 1979, report that FDA initiate a drug residue monitoring program for milk. A March 31, 1980, analysis by Dr. Mukund R. Parkhie, Acting Special Assistant to the Associate Director for Human Food Safety, noted that while a number of drugs are approved for use in lactating dairy cattle, "milk is being monitored by state and local governments and creamaries for only penicillin group of antibiotics." Five years later, Dr. Joseph A. Settepani wrote in a March 20, 1985, memorandum that "we should have a regulatory program to monitor for residues in milk drugs such as flukicides that the states do not look for in their monitoring programs." What steps, if any, has FDA initiated to ensure monitoring of all animal drug residues left in milk?

12. On July 12, 1985, Dr. Judith Hauswirth, a CVM toxicologist, advised the subcommittee staff that CVM's Cancer Assessment Committee concluded that ipronidazole was associated with an increase in malignant lung tumors in mice. The CAC was requested to conduct such a review in a June 21, 1983, Division of Toxicology memorandum. When did the CAC conduct its last meeting on the drug? Why has no memorandum been prepared of the CAC's findings and conclusions?

13. Has FDA calculated the "safe" levels for ipronidazole and dimetridazole corresponding to a cancer risk of 1 cancer in 1 million population, and, if so, please state what those levels are and when and by whom they were computed.

14. Dr. Crawford testified that CVM has taken steps to assure safe uses of ipronidazole and dimetridazole by requesting the sponsoring drug firms to develop acceptable detection methods. When did FDA ask these firms to develop detection methods capable of detecting residues at the "safe" level corresponding to a cancer risk of 1 cancer in 1

million population? Please supply copies of any and all agency requests for the development of such methods.

15. Dr. Crawford testified that at the insistence of some 27 different groups, including consumer groups, attending a September 1983 meeting, CVM modified the policy announced on August 1, 1983, that prohibited all extra-label uses of drugs given to food-producing animals. Please list all consumer groups participating in this meeting.

16. What are the levels of carbadox and its metabolites corresponding to a cancer risk of 1 cancer in 1 million population, and when did FDA calculate these levels? Has FDA requested the sponsor to develop an analytical method sufficiently sensitive to detect such levels, and, if so, when?

17. Dr. Crawford testified that some medicated blocks are being marketed that "are in the process of obtaining approval." Please identify all medicated blocks that are not the subject of an approved new animal drug application, and state the legal basis for permitting their continued marketing.

18. There are approximately 200 unapproved sulfa drugs currently being marketed. On July 22, 1974, FDA permitted these "new animal drugs" to be marketed without new drug approval if their sponsors submitted additional safety data. On July 5, 1984, FDA noted that few of these sponsors had submitted the data needed to ensure safe sulfa residue levels in edible products. On what legal basis has FDA now given these firms more than eleven years to market these new animal drugs without pre-market approval?

19. It is our understanding that the Animal Health Institute (AHI) has contracted to conduct the residue depletion studies needed to determine whether many unapproved new sulfa drug products can be approved. Have the protocols for these studies been submitted for FDA's review and, if so, when? Does FDA plan to initiate action to remove these drugs from the market if these studies are not submitted to the agency by October 7, 1985, the interim marketing termination date established by FDA in the July 5, 1984, Federal Register?

20. During an August 7, 1980, meeting, FDA's General Counsel stated that a 1977 proposal to permit interim marketing of unapproved teat dip products could not be finalized because the Federal court's decision in the Cutler v. Kennedy case rendered interim marketing arrangements illegal. Accordingly, as stated in a March 3, 1981, memorandum from Dr. Terence Harvey, then BVM's Deputy Director, the interim marketing proposal for teat dips was vacated. Why has FDA not similarly rescinded the interim marketing privileges it has granted for unapproved medicated blocks and sulfa drugs?

21. Did CVM receive a ruling from the Office of General Counsel prior to the initiation of the albendazole emergency INAD program stating that the Food, Drug, and Cosmetic Act authorized this program. If so, please provide a copy of that ruling.

22. A draft memorandum of FDA's January 17, 1985, meeting with SmithKline stated: "After the firm's [earlier] conference with Dr. Crawford regarding oncogenesis, etc., reference to safety concerns was excluded from the [albendazole] recall letter. . . Also, Dr. Theorides [a SmithKline scientist] has met with Dr. Crawford (at Cornell) this week to give Dr. Crawford an extensive briefing on carcinogenesis and the pathological significance of the Bio-Dynamics findings." Please provide all memoranda of Dr. Crawford's referenced meetings with the sponsor.

23. Dr. Crawford testified that he called the President of SmithKline one other time besides September 13, 1984, "to tell him to be sure that he was going to receive then a second letter which indicated that [albendazole] had to come off the market." Please state the date of this second call and provide any memorandum that was prepared of it.

24. In an October 6, 1982, review of the clorsulon rat carcinogenicity study, the Division of Toxicology found that

--the incidence of renal tubular adenoma together with adenocarcinomas was higher in the high dose male rats than in the pooled controls;

--the increase in renal tubular adenomas was statistically significant; and

--there was a statistically significant increase in renal epithelial hyperplasia in female rats at the mid and high dose levels.

In a September 21, 1983, review, the Division of Toxicology, after reviewing the historical control data submitted by the sponsor, "confirm[ed] the previous concerns expressed by" the division in its October 6, 1982, review. The September 21, 1983, review stated: "The biological significance of the kidney tumors observed in male and female rats at the mid and high dose levels need clarification from the CAC." However, on September 15, 1983, six days earlier, some members of the toxicology staff met and reportedly

> ". . . agreed with the firm's contention that the occurrence of kidney tubular adenoma observed in the high dose group was not drug-treatment-related and such rare tumors are commonly observed in aging rats. The historical control data submitted by the sponsor (letter dated January 21, 1983) and the data available in open literature in the test species supports the claim of the sponsor. The significant incidence in male rats of kidney epithelial hyperplasia at the mid dose level and hydronephrosis at the high dose level was also discussed at the meeting and it was agreed that these lesions were not pre-neoplastic but were considered as MK-401 treatment-related."

1. Since there is usually an increase in tumors associated with the aging process, what did FDA's toxicologists mean when they concluded the kidney tumors associated with administration of

clorsulon were "rare tumors [that] are commonly observed in aging rats"?

2. Please provide the record of FDA's review of the historical control data for kidney tumors in Sprague-Dawley rats provided by the sponsor, as well as that appearing in the literature? In addition, please provide all literature references concerning the incidence of such tumors relied upon by FDA reviewers.

3. If clorsulon's tumorigenic effects on the kidney were not drug-related, how does CVM account for statistically significant tumor increases in treated vs. untreated animals, particularly since clorsulon is structurally related to diuretic drugs [see Dr. Settepani's March 20, 1985, memorandum] known to have an effect on the kidney?

4. Please explain how, without reviewing the kidney slides, FDA was able to conclude that kidney epithelial hyperplasia and hydronephrosis were not pre-neoplastic.

25. On March 13, Dr. Zeeman advised the subcommittee staff that during a January 28 meeting, a Merck representative expressed his expectation that clorsulon would be approved that day. Because clorsulon labels had already been printed, he was not particularly receptive to Environmental Staff's suggestion that stickers be attached to these labels warning of the drug's potential phytotoxicity. Why didn't FDA at least require such warning stickers at the time of approval?

26. In addition to providing the date that clorsulon labels were modified to include an environmental warning statement, please supply the dates that such labels (1) were submitted to FDA for its approval and (2) went into user distribution channels.

27. In 1981, Government pathologists concluded that a veterinary drug subject to a pending NADA induced tumors in rat livers. Industry consultants, however, classified these "tumors" as "nodular hyperplasia." Subsequently, an independent peer review group was empanelled, which sided with the Government scientists in characterizing these lesions as tumors. Consequently, in the spring of 1983, the sponsor was advised by FDA that the drug could not be approved. In light of this case, why didn't CVM follow the Cancer Assessment Committee recommendation for an independent review of industry's contention that the liver lesions associated with administration of fenbendazole were "nodular hyperplasia" rather than tumors?

28. In view of fenbendazole's chemical similarity to albendazole, does FDA plan any further pathology review of the drug, as it has for thiabendazole?

29. When FDA decided to suspend regulatory action against feeds containing gentian violet, Dr. Gerald Guest wrote on December 14, 1981, that if safety studies confirmed the agency's suspicions that

gentian violet is carcinogenic, regulatory action against poultry feeds containing gentian violet would be reinstituted immediately. FDA's National Center for Toxicological Research (NCTR) concluded that gentian violet causes cancer in animals and should be considered an animal carcinogen. CVM's Cancer Assessment Committee unanimously concurred with this finding last November. In light of NCTR's and CVM's findings of carcinogenicity, why hasn't FDA resumed regulatory action against feeds containing gentian violet?

30. In an April 9, 1985, memorandum, Dr. Joseph Settepani wrote that agency attorney, Mr. Fred Degnan, "has never failed to point out that the Agency has a very small burden to successfully defend the position that a sponsored compound is not generally recognized as safe and that this burden appears to be clearly met by the results of the lifetime feeding study with gentian violet in mice." Inasmuch as two agency components have concluded that gentian violet is a carcinogen in at least one mammalian species, what is the legal basis for permitting its continued use in poultry feed?

31. In January 1985, CVM managers decided that FDA would issue a proposal in the Federal Register to declare gentian violet to be "not GRAS" if it determined that the compound should be prohibited for use in poultry feed. In a February 28, 1985, memorandum, Dr. Settepani wrote that such an option would probably have to be reviewed by the Department and OMB, which is likely to mean that it will be

> ". . . several years or longer before the Center is in a position to remove residues of this carcinogenic dye from our supply. How can we defend these delays to consumers when a much faster option ie., resume taking regulatory action, is available to the center. . . [W]e brought approximately 25 successful seizure actions and two successful injunctions during the 1960s and 70s when we only thought the dye was carcinogenic. Should we do any less now that we know the compound is carcinogenic and we know that residues above the one-in-one million lifetime risk level for cancer occur in the meat from treated birds?"

Why, in light of the delays such a proposal could entail, would FDA not merely initiate injunction and/or seizure actions on the grounds that gentian violet is an unapproved and hence illegal food additive when used as a mold inhibitor in poultry feed?

32. In an August 8, 1985, letter to Congressman Raymond J. McGrath, Commissioner Young stated that FDA would not take enforcement action against certain Vitamin K active substances (VKAS) used in animal feed that are neither covered by a prior sanction nor are generally recognized as safe (GRAS). FDA's enforcment plans notwithstanding, please explain how the marketing of these VKAS are consistent with the pre-market approval requirements of the Food, Drug, and Cosmetic Act.

33. In an April 9, 1985, memorandum, Dr. Settepani noted that there had been since 1981 a 50% decrease (from 14 to 7) in the number of toxicologists working on animal drug/human food safety issues. In that memorandum, Dr. Settepani wrote:

> ". . . The 50 percent reduction in toxicologists working on HFS [Human Food Safety] . . . has proven to be a real hardship. . . [T]he center has lost most of its expertise in several areas of toxicology. . . Differences of opinion often arise between drug sponsors and petitioner reviewers concerning interpretation of scientific data. When this happens, sponsors hire the best available experts on the subject to argue their side of the issue. When the Center lacks the necessary expertise to effectively counter these arguments we are in danger of not being able to insure that safe conditions of use of a candidate drug will be established."

Does CVM plan to request additional toxicological resources to carry out its responsibilities? If so, please elaborate.

34. FDA's current hearing to withdraw the nitrofurans from the market has diverted many agency personnel from other responsibilities. How many FTEs have been allocated to this function?

35. A June 1980 memorandum from Dr. Robert J. Scheuplein, Director, Food Animal Additives Staff, stated:

> "Because of existing adverse data, it is unlikely that even with additional testing safe conditions of use can be found for Carbadox, Dimetridazole, . . . and Ipronidazole. The approvals for those products are likely to be withdrawn."

Dr. Crawford, in fact, testified that CVM will be addressing the need to initiate administrative action against the approvals of these drugs. How many market withdrawal hearings can CVM convene in a year and carry on the level of activity it currently performs?

DOCUMENTS SUPPORTING THE SUBCOMMITTEE'S QUESTIONS THAT ARE NOT OTHERWISE INCLUDED IN THE HEARING RECORD FOLLOW:

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

The Acting Deputy Commissioner, HF-2 /s/ Sanford A. Miller January 14, 1980
Through: Director, Bureau of Foods ______

Cyclic Review
file

Director,
Food Animal Additives Staff, HFF-350

Briefing Memorandum on the Cyclic Review of Animal Drugs (for January 16th at Bureau of Foods)

The purpose of the meeting is to describe for Acting Deputy Commissioner Novitch, the Bureau of Foods recommendations for the Cyclic Review of Animal Drugs.

A. Need For a Cyclic Review

Most marketed animal drugs have been approved on the basis of safety evaluations currently considered inadequate. Toxicological concerns, testing protocols and the stringency of Bureau safety evaluations have all changed since the earliest animal drugs were approved, circa 1940. Nearly 40% were initially approved before 1958. Only 5% were initially approved after 1974. Three specific reasons for a thorough review are:

1. Evidence of possible human risk

Significant human safety concerns have arisen on an ad hoc basis over several approved animal drugs, e.g.

1. DES ------------------------cancer, hormonal effects
2. Nitrofurans-----------------cancer
3. MGA-------------------------cancer, progestational effects
4. Sulfonamides----------------cancer
5. Antibiotics-----------------drug resistance

Only by a systematic review will we be able to determine if other drugs present serious safety concerns.

2. Increased exposure

The development of the animal drug industry and the significant changes that have occurred in the rearing of animals for food production has resulted in an increased potential for human exposure to drug residues. Since "probable consumption is a vital part of any evaluation it is likely that increased marketing and distribution of some animal drugs can, per se, trigger a concern that would not otherwise be significant.

3. Inadequate data supporting safety

Nearly all approved animal drugs lack total residue depletion studies which are now regarded as essential for a safety evaluation. Also most approvals prior to 1974 were based in part on toxicological test protocols and chemical methods now considered inadequate. It is very likely that if all 195 approved drugs were reevaluated in the light of current science and policy (i.e., SOM and GFS), that several could not meet the "shown to be safe" standard and that many more would require revised tolerances.

Overall, the completion of the review should lower the risk from the use of animal drugs and establish greater public confidence in the adequacy of the agency's review process and in the safety of animal derived foods.

B. Scope of the Review

The Bureau considered two basic approaches to the review process:

1. A "paper review" - a review based entirely on available data like the DESI or GRAS reviews.
2. A review requiring (where necessary) the generation and submission of data currently essential for a scientific evaluation, e.g., the OTC drug review.

The first type of review would be easier to initiate and complete. However, since in most cases, the available data will be inadequate; section 512(e) of the act would require revocation of the approval of most NADA's. This approach would deprive the public and the food-producing industry of many animal drugs that could be shown to be safe through additional testing and could expect to be severely challenged.

The Bureau has therefore concluded that the only feasible approach is one which provides for the submission of the minimum data now considered essential for an adequate review and which permits continued marketing of the drug during the testing and evaluation period.

The first cycle of the review is expected to take approximately 8-10 years and to consist of three phases:

Phase 1. Evaluation of available data and required residue depletion studies. Agency actions taken to affirm or deny approvals on drugs requiring no further study.

Phase 2. Determination of test data required for specific "inconclusive" drugs. Scheduling of testing and submission of testing data necessary for the evaluation of "inconclusive" drugs.

Phase 3. Final agency action taken to affirm, deny or modify original approval.

In Phase I the drugs will be reviewed by a priority based on (1) whether the drug's structure raises carcinogenic concern, (2) the potential for human exposure to residues determined by use classification and (3) the date of first approval for the drug. If the safety evidence evaluated in the first phase of the review is inconclusive and there is a reasonable certainty that no harm will result from the drug's continued use, while the safety questions are being resolved by further testing, the drug will be permitted to remain on the market. In these situations, it may be advisable to amend the existing approval to require a longer withdrawal period or otherwise modify the use conditions to provide a greater margin of safety. Where additional testing is required to affirm safety, these tests will be scheduled in Phase II by a priority based upon human health significance.

In addition to this systematic cyclic review process the Bureau will continue to initiate actions whenever sufficient adverse information comes to our attention. There are approximately half a dozen drugs in this category currently in various stages of investigation, review or hearing preparation.

C. Stage of Completion

At a previous strategy session with Mr. Gardner on October 2, 1979 it was decided to develop an Advance Notice of Proposed Rulemaking outlining the intent, scope and purpose of the cyclic review of animal drugs. This was to be accompanied by a Proposed Rule requiring total residue studies and an economic impact statement. The first two of these documents have been prepared and the third is in preparation.

Robert J. Scheuplein, Ph.D.

cc: HFV-16 (2)
HFF-458
HFF-152
HFF-154
HFF-1, HFJ-5, HF-2 , HFF 310
R/D:HFF-350:RJScheuplein:rbs:1/13/80
F/T:rbs:11/14/80

The Commissioner July 9, 1980

Through: The Deputy Commissioner

Director, Bureau of Veterinary Medicine, HFV-1

Cyclic Review and SOM

I would like to share some parting thoughts on the above subjects. I believe the excellent briefing by Dr. Scheuplein July 2, finally set these two initiatives in perspective. Bob is to be soundly commended for a cogent and balanced presentation.

I philosophically endorse the notion of Cyclic Review and of SOM. As you know, I am something of a regulatory zealot, but I have learned at least one basic truth over the past two years: unless it is politically possible to regulate, no regulation will occur. Transcientific issues like saccharin, nitrite, and antibiotics in animal feed require subtle negotiation with virtually all elements of the society we serve. This is perhaps not the way it was meant to be or the way it should be, but it is the way that it is.

It is not economically possible for the animal drug industry to comply with Cyclic Review and SOM and it is unrealistic to expect the government to expend 35 to 50 million dollars on this undertaking. Therefore I believe the Congress would block Cyclic Review and SOM on the grounds that such an undertaking would be unnecessary, cost ineffective, and inimical to the livestock and pharmaceutical industries.

I think, however, that it is also clear that FDA must proceed with some version of periodic review. FDA would not be wise in any case to proceed until a defensible economic impact assessment is accomplished. Not even FDA can agree on the validity of the figures that were presented on July 2. Going public with those figures would be risky if not foolhardy. Eventually, the Agency will be forced into a fallback position on Cyclic Review - SOM. Falling back is going to be devilishly empirical without reliable cost figures.

The legal argument that we cannot countenance modification of Cyclic Review - SOM because of some vague historical commitment is without merit. This is the same as saying, "FDA cannot change its coporate mind." That kind of de rigeur "Let-them-eat-cake" attitude has brought the Agency most of the grief it has deserved over the past 75 years.

Lastly, I would respectfully suggest you order implementation of Cyclic Review and SOM be forestalled until a comprehensive analysis of the economic and public health impact of these initiatives can be performed. And I would be pleased to personally participate in any appropriate manner in the decision or in such studies as may be ordered.

AFTERTHOUGHT

We may have a situation here that is akin to the societal and ethical dilemmas occasioned by computer assisted axial tomography. That is to say, is the overall increase in health care costs caused by the utilization of the CAT-Scan worth the occasional unique indication for the instrumentation? Cyclic review - SOM may well imperil new animal drug research, dangerously shrink the veterinary medical armamentarium, and escalate livestock production costs. In short, Cyclic Review - SOM might prove to be well-intentioned public health imperatives that cannot be practically afforded. The quality of American life would be significantly compromised by a diminution of approved animal drugs and/or retardation of animal drug research.

Lester M Crawford, DVM,

Lester M. Crawford, D.V.M.

cc: Dr. Miller, HFF-1
Dr. Guest, HFV-9
Dr. Harvey, HFV-3
Dr. Scheuplein, HFF-350
gcm/7/8/80

DRUG RESIDUE MONITORING
IN
MILK

Mukund R. Parkhie, DVM, Ph.D.

Acting Special Assistant to the Associate Director
for
Human Food Safety
HFV-9, Bureau of Veterinary Medicine
Food and Drug Administration

March 31, 1980

Rockville, Maryland 20857

DRUG RESIDUE MONITORING IN MILK

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Drug Residue Monitoring in Milk

I. **Background** - The Commissioner FDA has appointed a committee to evaluate analytical methods which would quantitate residues in tissues of food producing animals resulting from approved drug usage as additives to feed per Section 21CFR558. The Committee reported (hereafter called Andres' Report) on the validity of tissue residue methods with regards to their determinative and confirmatory capabilities for regulatory process.

The Committee recommended to the Commissioner that "FDA should initiate a drug monitoring program for milk and eggs. These foods are in highest food volume category and span the total human life cycle."

II. **Issues** -

(1) Should milk be monitored for drug residues? If so, why? Which drugs are to be monitored in priority and why? How the monitoring program be initiated?

(2) Should assay methodologies be developed prior to undertaking surveillance of drug residues; simultaneously with surveillance program or after the results of this survey are reviewed and analyzed.

(3) What are the bases for the conclusions and the recommendations.

III. **Approaches to Issues** -

(1) Identify the new animal drugs which are approved for use in lactating dairy cattle and for which either determinative and/or confirmatory analytical methods are not available.

(2) Determine the impact of drug usage on human safety on the same principles as used in SOM document and in the Threshold Assessment Guidelines.

(3) Answer to the needs and philosophies of the Surveillance and Compliance wing of the Bureau in monitoring drug residues in milk.

IV. RESULTS

(A) Consultation - The findings reported herein include the recommendations of the key personnels from the Surveillance and Compliance directorate of the Bureau. Those consulted include: -

(a) In-house Consultations -

January 29, 1980:

Mr. Edward Ballitch, Director, Division of Compliance

February 6, 1980:

Dr. Max Crandall, Associate Director, Surveillance and Compliance.

Mr. Leon Brunk, Deputy Associate Director, Surveillance and Compliance.

Mr. Edward Ballitch, Director, Division of Compliance

March 7, 1980

Dr. Richard Griesemer, DVM, Ph.D.
Associate Director for Carcinogenesis
Carcinogenesis Testing Program
National Cancer Institute, NIH

Phone: - 496-5591

March 10, 1980

Dr. Jerrold M. Ward
C-TP, Room 402
Pathologist, Division of Cancer Research and Resources

Phone: - 496-6868

(B) Evaluation Criteria

The drugs will be evaluated using the same three criteria upon which SOM and Threshold Assessment Documents are based. These are (a) use of the drug: (b) amount of residue accumulation, and (c) Toxicological significance of the parent compound and/or of residue metabolite to human health.

(a) Use of the drug

The Andres' report identified about 42 drugs (categories II and III) for which no confirmatory methods are available to support regulatory missions of FDA. Thirty-six drugs from these forty-two lack, in addition, adequate determinative methods. An acceptable determinative method is available for the rest six.

Out of forty-two drugs, lacking suitable methodologies to support regulatory actions, the following are approved for use in lactating dairy cattle feeds. These are: -

Categories

I. **Antibiotics**

  1. Chlortetracycline

II. **Antibacterial**

  2. Sulfaethoxypyridazine

III. **Anthelmintics**

  3. Levamisole
  4. Thiabendazole
  5. Coumaphos

IV. **Defrothicant**

  6. Poloxalene

In addition to these drugs, the author would like to include the discussions on some of the following drugs. These drugs are: -

(1) Sulfonamides - sulfadimethoxine, and sulfamethazine

(2) Erythromycin

(3) Oxytetracycline, and

(4) Tylosin

(Note: - None of the aforementioned drugs have adequate determinative and/or confirmatory methods). The reasons for inclusion of these drugs are: -

(a) Usage of these compounds in lactating dairy cattle.

(b) Known mechanisms of their secretion into the milk, e.g. Sulfonamides.

(c) Routes of administration, other than medicated feed, which are likely to precipitate drug residues in milk, e.g. intramammary infusion products—erythromycin and oxytetracyclines.

(B) Residue Accumulation and Toxicological Significance

(1) Sulfonamides: -

(a) Sulfonamides have been shown to elicit neoplastic and carconogenic effects. (p. 1181, NIOSH Registry of Toxic Effects of Chemical Substances).

(b) However, at conc of 100 ug/ml no overt toxicity of sulfamethazine was observed in in vitro tissue culture system (FDA Contract #223-78-7040 - Final Report). This was true of the parent compound, sulfamethazine as well as its metabolite - acetylsulfamethazine.

(c) Sulfaethoxypyridazine has been placed in most concerned category (Cat. III) in the Drug Carry Over Document.

(2) Tetracyclines

(a) Tetracycline, in general, has been shown to be teratogenic (Brit. J. Dermatol. 76:374, 1964, for review, please see Internist 15(1): 7, 1974 and Yale J. Biol & Med. 48:377; 1975).

(b) Oxytetracycline has been shown to produce teratogenic effects in women and dogs (J. Am. Med. Assoc. 188: 178, 1964: Therapie 23: 1247, 1968; for Tox. Rev; please see, Am. J. Med. 38: 48, 1965).

(3) Anthelmintics

(a) Thiabendazole may not be of genetic risk to man concludes a recent review in mutation research (Mutation Res. 32(2):151, 1975).

(b) Levamisole Hydrochloride (1) Although levamisole as such has been reported to produce blood effects (Brit. Med. J. 20: 602; 1971), no such effects are reported for hydrochloride salt, which is used in veterinary medicine.

(2) Drug Carry Over Committee enlist levamisole as of the most concern; however, it is neither reported as a carcinogenic, mutagenic or teratogenic chemical. (1978, NIOSH Directory of Toxic Effects of Chemical Substances). The lowest published lethal concentration of levamisole hydrochloride to human per oral route, however, is 2 mg/kg (Toxicol. and Applied Pharmacol. 20: 602, 1971). Levamisole may be moderately toxic (Brit. Med. J. 20: 602; 1971) as assessed for cyclic review document, however, its soluble salt, (hydrochloride), is likely to be more toxic (Nature 209: 1084, 1966).

(c) Coumaphos: -

Although extremely toxic pesticide, coumaphos was not found to be carcinogenic in NCI bioassay chronic studies. (NCI Carcinogenesis Tech. Report No. 96).

CONCLUSIONS AND RECOMMENDATIONS

1. If monitoring of milk for drug residue, as recommended by Andres' Report, be carried out, the surveillance program for residue monitoring should be in the following order.

Category I

Sulfonamides (Sulfaethoxypyridazine, Sulfamethazine, Sulfadimethoxine)

Tetracycline (chlor and Oxytetracycline)

Category II

Erythromycin

Levamisole

Category III

Thiabendazole

Poloxalene

2. These recommendations are based upon the (a) Use of the drugs (2) likelihood of their residue accumulation in milk and (3) toxicological significance of these residues to humans.
3. Currently, milk is being monitored by state and local governments and creamaries for only penicillin group of antibiotics.
4. USDA monitors pesticides in milk and as such coumaphos may be under monitoring program.
5. Market Basket Survey program from the Bureau of Foods will be able to provide assistance in seeking milk samples.
6. Tracing the residue violated milk to its source will be a difficult task. More field personnel will be required.
7. This program, which is aimed to assure the safety of milk to humans, will require increased manpower and fund allocations to the Associate Director for Human Food Safety and EDRO.
8. Rapid screening techniques may be utilized for surveilling drug residues in milk using the priority scheme described above.
9. The results the survey may change the direction of monitoring of the drugs and will provide clues as to the drugs, where the need for development of methodologies for regulatory purposes, is urgent.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date June 21, 1983

From Division of Toxicology/BVM-HFV-330

Subject Two-year Oncogenicity Study of Ipronidazole Base, Ro 7-1554/000, in Mice

To Cancer Assessment Committee

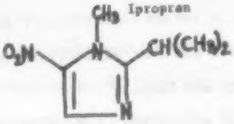
Common Name: Ipronidazole

Numerical Identification: CAS Registry No. 14885-29-1

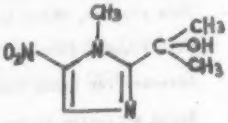
Chemical Name: 2-Isopropyl-1-methyl-5-nitroimidazole

Trade Name: Iprorpan

Structure:



Ipronidazole



Hydroxy metabolite

Use: Treatment and prevention of blackhead (histomoniasis) in turkeys. Antimicrobial for swine dysentery. For growth promotion and improved feed efficiency.

IMAD's and NADA's:

INAD 458	turkey
INAD 500	turkey
INAD 599	swine
INAD 1081	swine
INAD 1130	shrimp
NADA 43-477	turkey
NADA 91-782	turkey
NADA 92-443	swine
NADA 95-985	swine

Regulations:

1. 21 CFR 558.305 - approved for use in a 12.5% premix for turkeys. Do not feed to turkeys producing eggs for food.

a) 0.00625% in the feed of turkeys for prevention.

b) 0.025% in the feed of turkeys for 7 days followed by 0.00625% for treatment.

c) Withdrawal time prior to sacrifice for a) and b) 4 days.

2. 21 CFR 556.340 - No residues of ipronidazole or its hydroxy metabolite as determined by the approved regulatory method (sensitivity 2 ppb).

Background Toxicology Data

Acute Toxicity:

Species	Route	LD_{50} ± S.E. (mg/kg)
Mice	P.O.	970 ± 36
	I.P.	600 ± 83
	S.C.	400
Rats	P.O.	920 ± 48
Rabbits	P.O.	960 ± 95

Subacute Toxicity:

1. Species: Rat (8 per sex per group)

Levels: 0, 20, 80 and 320 mg/kg/day in the feed for 13 weeks.

Toxicity: a) males - body wt. depression 320 mg/kg
- hepatocellular hypertrophy 320 mg/kg

b) females - body wt. depression 320 mg/kg
- increased body wt. 20 & 80 mg/kg
- depressed ovarian wts. - all groups

No-effect level: males - 80 mg/kg
females - not determined

2. Species: Dog (4 per group)

Levels: 0, 20, 80 and 160 mg/kg by capsule for 13 weeks

Toxicity: a) 160 mg/kg group - 1st week, loss of appetite, body weight depression, muscle tumors, ataxia, dilation of pupils, lacrymation and salivation. 3 deaths - generalized congestion of organs, hepatomegaly, distension of gall bladder and alteration in bone marrow (hypocellular changes). Histology: fatty metamorphosis of liver, kidney vacuolation of epithelial lining of convoluted tubules.

b) 80 mg/kg dose - mild lacrymation and salivation, slight decrease of body weight, mild granularity of hepatic cell cytoplasm.

c) 20 mg/kg dose - no toxicity

No-effect level: 20 mg/kg

Teratology

1. Species: Rat (10 rats per group)
   Levels: 0, 1, 10, 100 mg/kg/day on days 7-16 of gestation
   Toxicity: None
   No-effect level: 100 mg/kg highest dose tested; study still under review pending revised data.
2. Species: Rabbit (5 per group)
   Levels: 0, 1, 10, 100 mg/kg/day orally by stomach tube
   Toxicity: 100 mg/kg - reduction in body weight, moderate sedation and increased number of resorptions
   No-effect level: 10 mg/kg

Three Generation Reproduction

Species: Rat
Levels: 0, 20, 200, 2000 ppm in diet
Toxicity: 2000 ppm - body wt. decreased in dams and males. Decreased litter size. Males - testicular changes.
No-effect level: 200 ppm

Chronic Studies

1. Species: Rat (50 per sex per group)
   Levels: 0, 20, 200, 2000 ppm in diet for 109 weeks
   Toxicity: females - decreased body wt. in 200 and 2000 ppm groups, significantly increased incidence of mammary tumors and of all tumors at 2000 ppm. males - no significant changes due to drug treatment.

No-effect level: not determined since it could be a tumorigen and/or carcinogen.

Study Title: Two-year Chronic Toxicity Study with Ro 7-1554/000 (Ipronidazole Base) in Dogs

Ipronidazole base was evaluated by long-term toxic effects and tumorigenic potential when administered in the diet of dogs.

Test Article: Ipronidazole free base. Purity is undesignated for one of the 2 batch numbers, but is given as 99% for the other as shown in the Hazleton mouse study.

Performing Laboratory: International Research and Development Corporation.

Dates of Study: November 7, 1977 to November 8, 1979.

Report Dated: November 4, 1981.

Animals: Purebred beagle dogs

No. of animals: 8/sex/group housed individually.

Animal Selection: Dogs were initially sorted by hand into groups with segregated littermates. The groups were statistically analyzed based on physical examination and serum chemistry and were then selected by random numbers. Two dogs of opposite sex that were littermates were placed in a group.

Route of Administration: Orally in the diet.

Dosage Levels: 0 (Group 1), 20 (Group 2), 200 (Group 3) and 2000 ppm (Group 4) which corresponded to average doses of 0, 0.47, 5.5 and 62 mg/kg/day for male dogs and 0, 0.57, 5.4 and 62 mg/kg/day for female dogs.

Dosing Period: 104 weeks.

Parameters Studied:

1. Appearance and Behavior - dogs were observed twice daily for changes in general behavior, appearance and signs of overt toxicity. General physical examinations were conducted once in pretest period and at 1, 2, 3, 6, 9, 12, 15, 18, 21 and 24 months.

2. Mortality and moribundity - observations twice daily.

READEX FICHE

3. Body weights were recorded weekly.

4. Food Consumption - recorded weekly and test material consumption was recorded weekly.

5. Ophthalmoscopic Examinations were performed for all dogs once during the pretest period and at 3, 6, 9, 12, 15, 18, 21 and 24 months.

6. Laboratory Analyses - Blood samples were taken for analysis twice during the pretest period and at months 3, 6, 9, 12, 15, 18, 21 and 24 months from all surviving dogs. An additional sample for hematology was required at 9 1/2 months "due to a probable technical error".

Urine was collected from fasting dogs overnight for 16 hours at pretest period, 3, 6, 9, 12 and 24 months, and for 24 hours at 15, 18 and 21 months.

A. Hematologic determinations included hemoglobin, hematocrit, erythrocyte count, total and differential leucocyte count, clotting time and prothrombin time.

B. Blood chemistry determinations included SGOT, SGPT, glucose, BUN, alkaline phosphatase, calcium, sodium, potassium and chloride.

C. Urinalysis included specific gravity, volume, color and appearance, microscopic examination of sediment, protein, pH, glucose, occult blood, nitrites, urobilinogen, ketones, bilirubin and albumin.

7. Organ Weights - an interim necropsy was conducted at 1 year on 2 randomly selected dogs/sex/group and necropsy was conducted on all survivors at 2 years and on 1 dog that died (week 99). At necropsy, the weight of the following organs was recorded: adrenals, brain, heart, kidneys, liver, lungs, spleen, pituitary, prostate/uterus, testes/ovaries and thyroid.

8. Histopathology - At necropsy, the following organs/tissues were collected from each animal and all except vertebra, femur and sternum were stained and examined microscopically.

adrenals (both)
brain (3 levels)
eye
gallbladder
heart
stomach
duodenum
lungs
mesenteric lymph node
skin
mammary gland
nerve
muscle
spleen

ileum
jejunum
cecum
colon
kidneys (both)
liver
urinary bladder
thyroid
femur
vertebra

pancreas
pituitary
prostate/uterus
costochondral junction
salivary gland
spinal cord (3 levels)
testes/ovaries
any gross lesions
sternum

Toxicity:

Treatment with ipronidazole at all dosage levels produced toxic signs of a varying nature including ptyalism, emesis, dermatitis, otitis, alopecia and depletion of body depot fat. At the dosage level of 2000 ppm, treatment for 6 months produced thinness in several dogs. At the conclusion of the study, males and females alike exhibited decreases of 4% in body weight in comparison to control dogs. Decreased food consumption occurred for all treated male groups during the initial year, but, at sporadic intervals throughout the study, for females of the 2000 ppm dosage group only. One male dog of the 2000 ppm dosage group expired with histologic evidence of lymphoid leukemia which is considered by DT to be unrelated to treatment.

Hematologic values were affected only in treated male dogs. Male dogs of the 2000 ppm dosage group exhibited statistically significant increases in segmented neutrophils, with corresponding decreases in lymphocytes, during the second year of treatment which was occasionally accompanied by slight statistically significant decreases in erythrocytes, hemoglobin and hematocrit. Alkaline phosphatase was markedly or moderately elevated in both sexes of the 2000 ppm dosage group throughout the study. In both sexes of this group, an elevation in SGPT and a depression in SGOT occurred only at the third month of treatment. Males of this group exhibited decreases in serum potassium throughout the study, while females exhibited decreases only after 6 and 9 months of treatment.

During the last third of the treatment period, dogs of both sexes exhibited sporadic abnormal urinalysis findings which included increased excretion of bilirubin, urobilinogen, protein, nitrites, glucose and a few instances of orange or brown-colored urine.

At necropsy, a dose-related decrease in depot fat was observed particularly in many dogs of both sexes of the 2000 ppm dosage group, but only in a few dogs of the 200 ppm dosage group. DT regards this effect to be related to treatment in the 2000 ppm dosage group only.

Statistically significant reductions in mean absolute weight were observed sporadically for prostate, testes and brain at termination, but are not considered directly related to treatment as relative weights did not vary correspondingly.

The livers of 1 control dog, 1 dog of the 20 and 200 ppm dosage groups and 7 dogs of the 2000 ppm dosage groups exhibited intracytoplasmic finely granular greenish-brown pigments in hepatocytes to a very slight-to-slight degree. No evidence of intracanalicular bile stasis or hepatocellular necrosis was evident. The slightly increased incidence of pigmentation in hepatocytes may be treatment-related. female 5.4 male 5.5 }

NEL: The "no-effect" level is 200 ppm (equivalent to 62 mg/kg) based upon observed decreased body weights and elevations in serum alkaline phosphatase and potassium at the dosage level of 2000 ppm.

Evaluation of Recently Performed Chronic Mouse Study

Study Title: Two-year Chronic Toxicity Study in Mice (Project 131-128)

Ipronidazole base was evaluated by long-term toxic effects and tumorigenic potential when administered in the diet of mice.

Test Article:	Ipronidazole free base of 99% purity.
Performing Laboratory:	Hazleton Laboratories America, Inc.
Dates of Study:	November 23, 1977 to October 18, 1979.
Report Dated:	October 22, 1981.
Animals:	Charles River CD-1 mice.
No. of Animals:	80/sex/group housed 5/sex/cage.
Animal Selection:	Mice were selected from 458 males and 460 females of 29 days of age acclimated previously for 14 days prior to initiation of the study.
Route of Administration:	Orally in the diet
Dosage Levels:	0 (Groups 1 and 2), 20 (Group 3), 200 (Group 4) and 1000 ppm (Group 5) which corresponds to 0, 2.6, 26 and 130 mg/kg/day for male mice and 0, 3.3, 34 and 170 mg/kg/day for female mice.
Dosing Period:	For males and females, 89 and 100 weeks, respectively, at attainment of 20% survival.

Parameters Studied:

1. Appearance and Behavior - gross signs of toxicity and

pharmacologic effects were recorded weekly during weeks 1-13 and biweekly thereafter.

2. Mortality and moribundity - daily observations. Survivors were analyzed statistically for males through week 89 and for females through week 100.

3. Body weights were recorded weekly for weeks 0-13 and biweekly thereafter. Data were analyzed for males at weeks 0, 2, 5, 12, 25 and 51 and for females at weeks 0, 3, 9, 15, 25 and 51.

4. Incidence and Sites of tumors - observations were recorded weekly for weeks 0-13 and biweekly thereafter.

5. Food Consumption - recorded weekly for weeks 0-13 and biweekly thereafter. Data were analyzed statistically for the total period of 0-51 weeks.

6. Ophthalmoscopic examination - performed grossly on all mice prior to treatment and thoroughly at week 5 and at termination, and thoroughly on 10 mice/sex/group at weeks 13, 26, 39, 52, 66, 78 and 91 (females only) and on any mouse exhibiting an abnormal finding in the previous period.

7. Gross Pathology - necropsies were performed on all mice found dead or killed in extremis and on all survivors at termination.

8. Histopathology - tissues were taken from 20 mice/sex of the control groups 1 and 2 and of the high dosage group (1000 ppm) and also on 2 mice of each additional dosage level. The latter mice were investigated because of the prevalence of dependant edema and ascites and also lesions of the heart and kidney. The following tissues were examined from the above groups: brain, thoracic spinal cord, pituitary, thyroid (parathyroids), thymus, adrenals, heart, kidneys, stomach, duodenum, jejunum, ileum, cecum, colon, pancreas, ovaries, gallbladder, uterus, testes, epididymides, prostate, lungs, spleen, liver, salivary glands, mesenteric lymph nodes, urinary bladder, nerve with muscle, eyes, bone marrow (femur), rib junction (costrochondral junction), skin with mammary gland, carcass and any unusual lesions. In addition, because of lung lesions noted in the 20/sex/groups of controls and 1000 ppm dosage groups, lung tissue was taken for microscopic examination from essentially all animals of each group.

9. Statistics - All statistical analyses were evaluated at the 5.0% probability level.

Results:

1. **Appearance and Behavior** - No effects associated with treatment were noted.

2. **Mortality** - During the initial 4 months only, male mice treated with 20 ppm (Group 3) exhibited a statistically significant decreased survival rate in comparison to controls (Groups 1 and 2). However, analysis of the completed study did not disclose any effects of treatment on survival.

Table 1
Survival

	Group 1		Group 2		Group 3		Group 4		Group 5	
Dosage Level:	0 ppm		0 ppm		20 ppm		200 ppm		1000 ppm	
Survivors:	No.	%	No.	%	No.	%	No.	%	No.	%
Males (at 89 weeks)	15	19	17	21	14	18	22	28	24	30
Females(at 100 weeks)	16	20	23	29	21	26	19	24	14	18

3. **Body Weights** - Individual body weight data is not given. At week 51, mean body weights and growth rates of all treated males did not differ significantly from those of either control group. For females, a significantly lower growth rate and mean body weight were noted for the 1000 ppm dosage group (Group 5) only in comparison to control Group 1. However, these groups differed significantly at Week 0. Growth rates for the 200 ppm dosage group (Group 4) and control Group 2 were also slightly (significantly) lower than that of control Group 1. DT does not consider these differences, with respect to only one of the control groups, to be treatment-related. No treatment-related differences from controls were evident to DT for the remainder of the study, although statistical analysis was not provided.

4. **Incidences and Sites of Tumors**

A. Pulmonary Lesions

Male and female mice of the 1000 ppm dosage group (Group 5) exhibited an increased incidence of hyperplastic and neoplastic lesions of lung in comparison to controls. For lungs of nearly all mice, incidences are shown in Table 2. For termination, the firm reports that 34.6% of male mice and 26.6% of female mice had lung lesions in contrast to control values of 12.7% for males and 8.2% for females. The incidences of such lesions in the 20 and 200 ppm dosage groups were not significantly different from those of the control groups. These lesions were composed primarily of focal alveolar/bronchiolar cell hyperplasia and alveolar/bronchiolar adenomas with a lesser incidence of alveolar/bronchiolar carcinomas. Individual mice, especially in the 1000 ppm dosage group, sometimes had more than one type of lesion.

The firm has included historical control data from 9 studies conducted during 1975-1980 with the same strain of mouse for which the incidences of "pulmonary neoplasia" were noted to vary from 6-75% for males and from 6-70% for females (Tables 3 and 4).

B. Additional Neoplasias

Incidences of histologically-confirmed neoplasias at sites on other organs and tissues are shown in Table 5. (Data are also included for lung neoplasia of those mice posted for complete histopathologic examination.) No treatment-related trends are evident aside from lung neoplasias.

5. Food Consumption - unaffected by treatment

6. Ophthalmoscopic Examination - No effects associated with treatment were noted and incidental findings were similar in all groups.

7. Gross Pathology - No treatment-related effects were found by gross pathological examination of the mice found dead, killed in extremis or killed at termination. The variety of changes and lesions observed in the organs or tissues were of the types commonly found in mice of this strain and age.

8. Histopathology Other Than Neoplasia

Control and treated groups exhibited similar spontaneous diseases and lesions. Amyloidosis and collid cysts were frequently observed in thyroid. Adrenals from many mice also exhibited amyloidosis. Heart sections occasionally exhibited amyloidosis, nonsuppurative myocarditis, aortitis and atrial thrombi. Many lung specimens exhibited perivascular, peribronchial lymphoid hyperplasia and focal pneumonitis. Spleen sections exhibited amyloidosis in many mice. Microgranulomas and amyloidosis were the commonest lesions observed in liver. The most frequent observations in kidney were focal nephritis, perivascular lymphoid foci and amyloidosis.

In sections of gastrointestinal tract, amyloidosis was fairly commonly observed in the small intestine and occurred less frequently in the stomach and large intestine. Occasional nemotode parasites were noted in the colon. In the mesenteric lymph nodes, amyloidosis and lymphoreticular cell proliferation were the commonest findings. Renal amyloidosis in conjunction with atrial thrombi was also noted. In testes, occassional incidences of hypospermatogenesis and amyloidosis were observed. In ovaries, ovarian or paraovarian cysts were often noted and cystic endometrial hyperplasia was sometimes present in uterus. Various other spontaneous disease lesions and incidental findings were observed, but none were treatment-related with the exception of the above findings in lung.

Discussion

The no-effect level for this study has been reported by the firm as 200 ppm (equivalent to 26 and 34 mg/kg/day for male and female mice, respectively) based on the prevalence of pulmonary neoplasia observed at a dosage level of 1000 ppm. No indications of a treatment-related effect were observed in regard to mortality, clinical signs, body weight, growth rate, food consumption, ophthalmoscopic findings and gross pathology.

CAC is requested to review the findings on lung neoplasia in the mouse study in conjunction with the historical controls provided by the firm.

Leonard D. Saalew
Leonard D. Saalew, Ph.D.

cc: HFV-16 (3)
HFV-300
HFV-320
HFV-340

Table 2
Incidence of Histologically Proven Lung Neoplasia
Chronic Toxicity Study of Ipronidazole Base (Ro 7-1554) in Mice

ORGAN DESCRIPTION	Groups: Dose Level (ppm) :	1 / 0	2 / 0	3 / 20	4 / 200	5 / 1000
				Males		
Total number of animals from which lung sections were examined		79	79	77	78	78
Alveolar/bronchiolar hyperplasia		8	8	3	11	37
Animals with primary lung neoplasms		11	9	10	13	27
Alveolar/bronchiolar adenoma		8	8	7	13	25
Alveolar/bronchiolar adenoma (multiple)[a]		0	2	1	2	6
Alveolar/bronchiolar carcinoma		3	2	3	1	7
Alveolar/bronchiolar carcinoma (multiple)[a]		0	0	0	0	1
Alveolar/bronchiolar adenoma and carcinoma		0	1	0	1	5
PERCENT OBSERVED (%)						
Primary Neoplasms		$\frac{11}{79}$ (13.9)	$\frac{9}{79}$ (11.4)	$\frac{10}{77}$ (13.0)	$\frac{13}{78}$ (16.7)	$\frac{27}{78}$ (34.6)
Adenoma		$\frac{8}{79}$ (10.1)	$\frac{8}{79}$ (10.1)	$\frac{7}{77}$ (9.1)	$\frac{13}{78}$ (16.7)	$\frac{25}{78}$ (32.1)
Carcinoma		$\frac{3}{79}$ (3.8)	$\frac{2}{79}$ (2.5)	$\frac{3}{77}$ (3.9)	$\frac{1}{78}$ (1.3)	$\frac{7}{78}$ (9.0)
Hyperplasia		$\frac{8}{79}$ (10.1)	$\frac{8}{79}$ (10.1)	$\frac{3}{77}$ (3.9)	$\frac{11}{78}$ (14.1)	$\frac{37}{78}$ (47.4)

[a] These mice are included in the totals for animals with adenoma or carcinoma.

Table 2A
Incidence of Histologically Proven Lung Neoplasia
Chronic Toxicity Study of Ipronidazole Base (Ro 7-1554) in Mice

	Females				
ORGAN DESCRIPTION Groups: / Dose Level (ppm):	1 / 0	2 / 0	3 / 20	4 / 200	5 / 1000
Total number of animals from which lung sections were examined	79	79	80	79	79
Alveolar/bronchiolar hyperplasia	8	6	4	8	18
Animals with primary lung neoplasms	5	8	3	6	21
Alveolar/bronchiolar adenoma	5	5	3	4	20
Alveolar/bronchiolar adenoma (multiple)[a]	0	0	1	0	5
Alveolar/bronchiolar carcinoma	0	3	0	3	2
Alveolar/bronchiolar carcinoma (multiple)[a]	0	0	0	0	1
Alveolar/bronchiolar adenoma and carcinoma	0	0	0	1	1
PERCENT OBSERVED (%)					
Primary Neoplasms	5/79 (6.3)	8/79 (10.1)	3/80 (3.8)	6/79 (7.6)	21/79 (26.6)
Adenoma	5/79 (6.3)	5/79 (6.3)	3/80 (3.8)	4/79 (5.1)	20/79 (25.3)
Carcinoma	0/79 (0)	3/79 (3.8)	0/80 (0)	3/79 (3.8)	2/79 (2.5)
Hyperplasia	8/79 (10.1)	6/79 (7.6)	4/80 (5.0)	8/79 (10.1)	18/79 (22.8)

[a] These mice are included in the totals for animals with adenoma or carcinoma.

August 7 1980

MEMORANDUM OF CONFERENCE

ATTENDEES: Dr. Crandall, HFV-200
Mr. Brunk HFV-200
Dr. Graves HFV-210
Dr. Beaulieu HFV-210
Dr. Scarr HFV-214
Dr Meyers HFV-216
Ms. B. April GCF- 1

SUBJECT: Teat Dips

The meeting was called to determine the present status and options for future consideration relative to the F.R. proposed rule on teat dips.

Ms April said that she intends to raise the teat dip interim marketing issue with Nancy L. Buc and that she could not provide a final GC opinion at this time. She stated her current opinion that the proposed final rule was not acceptable under Cutler v. Kennedy because of the provision for interim market. Further, she stated that an alternative may be to publish a tentative final rule deleting the interim marketing provision and providing an opportunity for comment on that change She said that based on her understanding of BVM's concerns regarding the deletion of the interim marketing provision, she has been considering what types of statements may be appropriate to make as to factors affecting whether we might take regulatory action and the timing of such action.

Mr. Brunk suggested that since the courts have said that we have discretionary privileges regarding enforcement, we might publish a notice that dips are NAD and follow with a Compliance Policy Guide as a means of compliance with the least disruption of existing practices in the entire dairy industry. We need to find out how to proceed as an agency, then present the human health aspects to Bureau of Foods. Since Bureau of Foods has said in relation to neomycin that they didn't want to publish guidelines but would review an individual NADA on its own merits, perhaps the same would apply to dips.

Dr. Crandall asked that GC respond by Sept. 25 with the best route to go so that a meeting can be scheduled about Oct. 1 with BVM, Bureau of Foods and GC.

Ms. April said she would present the problem to Nancy L. Buc and try to respond by that date.

Howard Meyers, D.V.M.
Chief, Non-Food Producing
Animal Branch
Division of Surveillance

cc: HFV-210, SDRF
HFV-200, Dr. Crandall
HFV-200, Mr. Brunk
HFV-210, Dr Graves,
HFV-210, Dr. Beaulieu
HFV-214, Dr Scarr
HFV-100, Dr. Baldwin
HFV-125, Dr Jacobs
GCF- 1, Ms. April
HMeyers ab:8/26/8008

Tickle File
1 Apr 81

Acting Director, BVM, HFV-1 March 3, 1981

Deputy Director, BVM, HFV-2

Teat Dip F.R. Notice - Executive Order 12291

On March 2, 1981, I met with Ms. April, Mr. Geyer, Mr. Stribling, Mr. Brunk, Drs. Crandall, Scarr, Beaulieu, Carnevale, and Jacobs to discuss the status of the August, 1977 proposal to codify our position that teat dips are new animal drugs requiring an approved NADA. This proposal included an interim marketing provision for these products.

In view of the Cutler decision and other points including lack of enforcement action on this stance for those teat dip products for which no adverse information is available, we collectively concluded that the teat dip proposal should be vacated. The Bureau believes that teat dips are in fact new animal drugs; however, they as a product class, do not warrant attempting to pursue codifying our position by this or any other regulation.

Instead, I recommend that we prepare a Compliance policy Guide indicating that such products will be dealt with on a case-by-case basis. Furthermore, regulatory action may be deferred unless a product is shown to present a clear and present danger to public health. This approach is necessary to utilize our resources for more pressing regulatory needs and relegate teat dips to a lower compliance priority. A like CPG is in preparation for udder washes. After CPG finalization we could publish their availability.

Additionally, in conjuction with Executive Order No. 12291, Federal Regulation, I recommend the teat dip proposal be vacated under this directive and Secretary Schweiker's instructions of February 10, 1981, as it is the most expedient route. I am aware that other Bureau proposals will have to be addressed under this order but the teat dip proposal should be one of the first to go.

Terence Harvey, Deputy Director
Bureau of Veterinary Medicine

Terence Harvey, D.V.M.

cc: Dr. Crandall, HFV-200 ✓
Dr. Scarr, HFV-214
Mr. Stribling, GCF-1
Ms. April, GCF-1
THarvey/gcm/3/3/81

DRAFT
#1

MEMORANDUM OF MEETING

January 17, 1985

Attendees:

SmithKline/Norden

Helen Birkhead, Manager, Regulatory Affairs, SKAHP
Jack Jordan, Attorney, SKAHP
R. M. Grossman, Manager Pharmacy QC/QA, Norden
Cecil R. Miller, Manager Technical Service, Norden
George Grass, Vice President, Pharmacy Development, Norden

Food and Drug Administration

Dr. William B. Bixler
Dr. Marin Norcross
Mr. Gary Dykstra
Dr. Paul Lepore
Mr. John Hauser
Mr. Edward Ballitch
Mr. Arthur Tsien
Dr. Norman Tufts

Subject: Albendazole INAD's

Firm INAD count totalled 17; FDA INAD count came to 21 plus 3 NADA applications.

Discussion began on the issue of withdrawal versus termination of INAD's, with the firm expressing concern in regard to data confidentiality, particularly if the data were "abandoned." Reassurance was given the firm that valid data from a terminated INAD could be transferred to an NADA or another INAD, as the case might be, and that these data would remain confidential. The firm is to consider that option and, if they agree that adequate protection was afforded, would be receptive to the INAD termination/data transfer plan.

Discussion of recall revealed the firm had issued recall notices to veterinarian purchasers dating back 18 months. In an earlier December 26 letter to 925 veterinarians requesting an inventory check, the inventory found was 2,820 tubes and 2,085 gallons in stock.

Despite SmithKline's claim that only veterinarians received the recall notice because Norden shipped only to veterinarians, our records do not substantiate the sales-to-veterinarians-only, which makes this recall one for mandatory close monitoring so as to include non-veterinarian sales.

The firm estimates 90% of the recall will be complete within three to four weeks, with all outstanding stocks of albendazole returned to Lincoln, Nebraska, by April 12, 1985, Salesmen will be making two rounds for check ups in that time, as worked out with Kansas City District Office. Kansas City district office will be advised of progress biweekley by Norden. Dosage forms shipped by SKAHP will also require monitoring.

After the firm's conference with Dr. Crawford regarding oncoghenesis, etc., reference to safety concerns was excluded from the recall letter. The firm does not agree with the Agency's decision that albendazole is an oncogen. Indeed, a panel of four firm-picked pathologists is reviewing the Bio-Dynamic rat slides at this time with the view to contesting the Agency oncogenesis-carcinogenesis decision. Also, Dr. Theorides has met with Dr. Crawford (at Cornell) this week to give Dr. Crawford an extensive briefing on carcinogenesis and the pathological significance of the Bio-Dynamics findings.

FDA called for complete termination of all INAD's, not just the emergency ones, a viewpoint not shared by the firm(s); and in Mr. Blanchard's letter of January 14, 1985, to Dr. Crawford, the firm refused to cancel all INAD's.

Despite FDA's insistance that the albendazole regimen under the INAD's was out of control, the firm continued to protest that such was not the case. Only after briefly discussing several instances of investigational distribution problems did agreement come for termination of all INAD's, with valid data to be protected as to confidentiality, and transferred to a limited number of other INAD's/NADA's for a new effort to generate data within an adequately controlled program.

Dr. Bixler and Mr. Dykstra are to be the contact persons for S&C, Dr. Norcross for NADE, and Kansas City district office for the recall.

Considerable discussion was held in regard to so-called "compassionate drugs" and "university-assisted rsearch." Despite any feelings to the contrary, authorization for these uncontrolled uses of drugs are not provided for in the regulations; and, contrary to the firm's expressed opinions, these uses had indeed resulted in documented case of misuse and loss of regulatory control.

Despite INAD restrictions, the firm was shown to have commercialized "flukicide" sales of albendazole, even selling the product via telephone, and for frankly extra-label use as a tapeworm remedy with no data generation. Nevertheless, SmithKline stoutly maintained that FDA had given them written permission in 1979 to go commercial (which is not provided for in the regulations).

All discussion aside, the FDA goal was to clean the slate and make a fresh, regulations-compatible start using new INAD numbers, fewer in number, such that adequate control could be assured, said control to be documented by FDA inspections.

The firm(s) stated the desirability of retaining momentum in several albendazole investigational areas, including premix, pellets, paste, suspension, perhaps boluses, and the IR-4 area.

These INAD's were selected for retaining and renumbering:

INAD 1641 - cattle suspension
INAD 2901 - premix
INAD 1928 - paste-cattle
INAD 1733 - sheep
INAD 2058 - bolus-cattle
~~INAD (IR-4)~~
(INAD 1999 - confined ruminants
and IR-4.

Albendazole shipments would cease until recall effectiveness has been checked and new INAD numbers assigned.

The problem of compassionate drugs and university assisted research,as they relate to lack of a regulatory basis, remained for further consideration by the Center on an industry-wide basis.

A question as to disposal of recalled albendazole brought the SKAHP response that "an incineration permit" had been filed, presumably for the recalled albendazole, although such a definitive statement was not heard.

Dr. Norman R. Tufts

cc: FDA Attendees
HFV-1
HFV-234(Baker)
HFR-7100
HFR-3100
NRTufts:km:1/22/85

DEPARTMENT OF HEALTH & HUMAN SERVICES

HFV-16

Memorandum

Date October 6, 1982

From Division of Toxicology/BVM
HFV-330

Subject MK-401

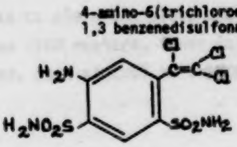
To Division of Food Animal Additives/BVM
HFV-320

INVESTIGATIONAL NEW ANIMAL DRUG NO. 2758(DCO (Submission dated April 27, 1982)	Merck, Sharp & Dohme Co. 125 E. Lincoln Ave. Rahway, NJ 07065 (AF# 12-611)
Proposed Use:	The sponsor intends to use the compound as a flukecide in cattle

I. Identity:

A. Chemical Name: 4-amino-6(trichloroethenyl) 1,3 benzenedisulfonamide

B. Structure:



C. M. W. 380.66

II. Use in Target Animals

A. Pharmacological Action:	Flukecide
B. Route of Administration:	Oral, by drench
C. Dose:	Up to 15 mg/kg in a single dose
D. Target Animal:	Cattle
E. Proposed withdrawal time:	28 days

III. Toxicological Studies

A. Acute Toxicity Studies

Species:	Route of Administration	LD_{50} mg/kg
Mouse	oral	> 20,000
Mouse	i.p. M	678(621-737)
Mouse	i.p. F	761(712-813)
Rat	oral	> 20,000
Rat	i.p. M	938(844-1043)
Rat	i.p. F	845(744-922)

1.	Dose levels Mouse	oral	2500, 5000, 10000, 20000 mg/kg
		i.p.	417, 500, 600, 720, 865 mg/kg
	Rat	oral	2500, 5000, 10000 mg/kg
2.	Vehicle:		1% aqueous methylcellulose
3.	No/Sex/Group:		10
4.	Observation Period:		14 days
5.	Toxicity:		Decreased activity, bradypnea and ptosis
6.	Evaluation:		The studies were adequate to assess the acute toxicity of MK-401

B. Twenty Nine Day Oral Range Finding Study in Dogs

Performing Laboratory:	Merck, Sharp & Dohme Research Laboratories West Point, Pa.
Species/Strain:	Dog/Beagle
No. of Animals/ Sex/Dose:	2
Weight range:	7.7-11.9 kg

Dose Levels:	0, 25, 100, 300, 900 mg/kg
Route of Administration:	Oral in capsules
Duration:	20 days for low and mid-dose; 29 days for the 100 mg/kg group, and 9-10 days for the two high dose groups.

Method:

Animals were presented the compound in oral gelatin capsules at doses of 100 mg/kg; 300 mg/kg; and 900 mg/kg for 9 days. The control animals received empty gelatin capsules. Nine days after initiation of the study two additional groups of one male and one female were placed on study at 25 and 50 mg/kg/day because of apparent toxicity at each of the initial dose levels.

The following changes in dosing regimen were undertaken in an attempt to reduce or prevent the emesis which occurred during or immediately following dosing in dogs from the 300 and 900 mg/kg/day groups; the drug was administered twice daily as a divided dose to dogs from the 100 mg/kg/day group on Drug Days 4 through 29, and to dogs from the 300 and 900 mg/kg/day groups on Drug Days 4 through 9. Also, on Drug Day 10 and/or 11, dogs from the 300 and 900 mg/kg/day groups received the compound by gastric intubation as a aqueous suspension in 0.5 percent methylcellulose (400 cps) at a volume of 5 ml/kg.

Observations

Physical signs:	daily
Body weight:	twice weekly
Food Consumption:	daily
24 hour H_2O intake/urine output:	Drug week 2, 3, and 4 on dogs from the control and 100 mg/kg group; drug week 1, 2, 3 from the 25 and 50 mg/kg/day group.

Hematology consisting of Hgb; ESR; RBC; MCV; leucocyte counts, total and differential; prothrombin time; platelets; Hct; MCH; MCHC:	Day 10 and day 28, control and 100 mg/kg groups. Day 8, 13 and 19-25 and 50 mg/kg groups.
Clinical chemistry consisting of glucose; BUN; creatinine, total protein; albumin; SGOT; SGPT; alkaline phosphatase; Na$^+$, K$^+$; Cl$^-$:	Same schedule as hematology
Urinalysis of protein; glucose, bilirubin, occult blood; sediment:	Days 10, 11, 28 and 29 - control and 100 mg/kg group Days 8, 13, 19, 20-25 mg/kg and 50 mg/kg groups
Gross post mortem examination on all dogs:	At termination of study
Organ weight of brain, testes, kidney, liver, adrenal, heart, on all dogs:	At termination of study

The following tissues were examined histologically from all dogs at termination of the study: salivary glands, stomach, small intestine, large intestine, liver, gall bladder, pancreas, adrenal, parathyroid, kidney, ureter, urinary bladder, ovary, uterus, testis and epididymis, prostate, skin, mammary gland, lung, heart, spleen, lymph node, thymus, bone marrow, bone, skeletal muscle, brain, spinal cord, nerve eye.

Results

1. All dogs in the two highest dose groups were sacrificed because of poor condition. No other mortality occurred. Emesis, ataxia, anorexia, decreased activity and dehydration were observed at all dose levels over 50 mg/kg. Hematuria was observed in high dose dogs. Dogs at the three highest dose levels showed body weight losses.

2. Leucopenia was observed in dogs at the three highest dose levels as well as an increase in ESR in one 100 mg/kg dosed dog on Day 10. No other significant changes in hematocrit were reported.

3. Several changes in biochemical parameters occurred in dogs dosed at 100 mg/kg or higher; increases in BUN and SGPT; decreases in alkaline phosphatase, SGOT, sodium, potassium and chloride.

4. Increase in urinary protein, glucose, leucocytes and erythrocytes occurred in dogs receiving 300 and 900 mg/kg of the compound. Blood was found in the urine of those animals.

5. Gross morphological changes occurred in dogs treated with 100 mg/kg or more of MK-401. The changes include: focal hemorrhage of heart, kidney, lymph nodes, gastrointestinal tract; necrosis of the ureters; hepatic hemosiderosis; perivascular cellular infiltration of the choroid plexus; edema of the choroid plexus, and vascular necrosis of the choroid plexus. Organ weight data showed an increase of absolute and relative liver weight at 100 mg/kg and above of MK-401.

Conclusion

Based on the hematological, biochemical and gross morphological changes observed in this study, 50 mg/kg is the no effect level.

C. Thirty-One Day Oral Range Finding Study in Rats

Performing Laboratory:	Merck Sharp & Dohme Research Laboratory West Point, Pa.
Species/Strain:	Rat/Charles River
No. of Animals/ sex/group:	5
Weight Range:	59-87 grams
Dose Levels:	0, 100, 300, 900 mg/kg
Vehicle:	0.5% aqueous methylcellulose

Route of Administration:	**Oral, by gavage**

Observations

Physical signs:	**daily**
Body Weight:	**pretest; days 4, 8, 11, 16, 19, 22, 25 and 29**
Hematology determinations of Hgb; Hct; ESR; RBC; MCV; WBC total and differential; clotting time; platelets; MCH; MCHC:	**Day 29**
Biochemistry consisting of glucose, BUN, albumin, total protein, SGPT, alkaline phosphatase, Na^+, K^+, Cl:	**Day 30**
Organ weights of liver, kidney, heart, spleen, brain, testes:	**At termination**
Gross examination of all rats:	**At termination**
Microscopic examination of the following tissues in control and high dose groups: adrenal, bone, brain, eye, ear, joint, nerve, liver, thyroid, parathyroid, pituitary, pancreas, salivary gland, small and large intestine, stomach, spinal cord:	**At termination**
Liver and all gross changes on all animals:	**At termination**

Results

1. All animals survived the study. Salivation occurred in animals at all dose levels. No other physical signs were reported. There was a statistically significant retardation of body weight in males at the mid and high dose levels. No adverse effect on body weight was observed in the females.

2. All hematology values reported in the treated animals were comparable to those of the concurrent and treated controls.

3. There was a significant increase in alkaline phosphatase activity in males at 300 mg/kg and in both sexes at 900 mg/kg. No other changes were reported.

4. Significant differences from the controls in absolute and relative organ weights were seen in the mid and high dose groups relative to brain, kidney, liver and testes. No other gross abnormalities were seen. Histologically, there was enlargement of hepatocytes in all high dose and one mid dose rats. No other changes were reported.

Conclusion

The thirty-one day oral range finding study was adequately performed, with a no-effect level of 50 mg/kg.

D. Fourteen Week Oral Toxicity Study in Dogs

Performing Laboratory:	Merck Sharp & Dohme Research Laboratory
Species/Strain:	Dog/Beagle
No/Sex/Group:	3
Age/Wt. At Start Of Study:	10-12 months; 7.9-13.6 kg
Route of Administration:	Oral, in capsules
Dose Levels:	0, 2, 8, 32 mg/kg/day

Observations

Physical appearance:	daily

Body Weight:	Pretest and twice weekly
EKG:	Pretest, weeks 4, 8 and 13
Opthalmology:	Pretest, weeks 4, 9 and 13
Hematology consisting of Hgb; RBC; MCV; WBC, total and differential, clotting time, prothrombin time, platelet estimation, Hct, MCH, MCHC:	Pretest, weeks 4, 8 and 13
Biochemical determinations of glucose, BUN, creatinine, total protein, albumin, SGOT, SGPT, alkaline phosphatase, bilirubin (total direct and indirect) Na^+, K^+, Cl^-, T_3 uptake, T_4 level:	Pretest, weeks 4, 8, and 13
Urinalysis consisting of protein, glucose, bilirubin, occult blood, sediment:	Weeks 4, 8, and 13
Gross necropsy of all animals:	At termination of the study
Organ weights of liver, kidney, testes, brain, heart, adrenal glands, thyroids:	At termination of the study

The following tissues were examined histologically from all dogs in the control and high dose groups at termination of the study: salivary gland, stomach, small and large intestine, liver, gall bladder, pancreas, adrenal, parathyroid, pituitary, thyroid, kidney, urinary bladder, ovary, uterus, testis and epididymis, prostate, skin, mammary gland, lung, heart, spleen, lymph node, thymus, bone marrow, bone, brain, spinal cord, nerve, eye.

The following tissues were examined histologically in all dogs: bone, marrow, liver, spleen, thyroid, parathyroid and all gross changes.

Results

1. No drug related physical changes were observed and all dogs survived the study. No drug induced EKG changes were seen. There were no ophthalmologic lesions. There was a slight loss of weight among the high dose females.

2. All hematology values were within the normal range except for one high dose dog which showed significant changes in Hgb, Hct, ESR, WBC and neutrophils at the end of the study. Similar changes occurred in one dog treated at the low dose level at week 8. The values in this dog were normal at the end of the study.

3. No adverse effects which could be attributed to drug administration were apparent on the biochemical parameters measured. No drug related urinalysis changes occurred.

4. No gross morphological changes were reported among the drug treated animals. There was a significant decrease in absolute and relative thyroid weight at 8 mg/kg and 32 mg/kg. There was a significant increase in absolute liver weight as well as organ/brain weight ratio in high dose male dogs.

5. No histopathological lesions were observed in the thyroid gland. One mid dose and one high dose male showed nodular hyperplasia of the spleen. One high dose male showed focal prostatic hyperplasia, and one showed erythroid and myeloid hyperplasia.

Conclusion

Based on the changes in thyroid and liver weight at the mid and high dose, and the hyperplasia noted at those dose levels, the no effect level for this study is 2 mg/kg.

E. Fourteen Week Oral Toxicity Study in Dogs

Performing Laboratory:	Merck Sharp & Dohme Research Laboratories West Point, Pa.

Species/Strain:	Dog/Beagle
No/Sex/Group:	3
Age at Start of Study:	10-11 months
Weight:	7.6-11.4 kg
Dose Levels:	0, 55 mg/kg
Route of Administration:	Oral, in capsules
Observations	
Physical Signs:	Daily
EKG examinations:	Pretest, and drug weeks 4, 8, and 13
Ophthmologic examinations:	Pretest, and drug weeks 4, 8, and 13
Hematology consisting of the following: Hgb; RBC; MCV; ESR; WBC total and differential, clotting time, prothrombin time, platelets, Hct, MCH, MCHC:	Pretest, and during drug weeks 4, 8, 13
Biochemistry consisting of glucose, BUN, creatinine, total protein, albumin, SGOT, SGPT, alkaline phosphatase, bilirubin (total, direct and indirect) Na^+, K^+, Cl^-, T_3 uptake, T_4 levels:	
Urinalysis consisting of protein, glucose, bilirubin, occult blood, sediment:	Pretest; weeks 4, 8, and 13

Gross necropsy on all dogs:	At termination of the study
Organ weights on all dogs: liver, kidney, testes, brain, heart, adrenal glands, thyroids:	At termination of the study

The following tissues were examined histologically from all animals at termination of the study: salivary gland, stomach, small intestine, large intestine, liver, gall bladder, pancreas, peritoneum, adrenal, parathyroid, pituitary, thyroid, kidney, urinary bladder, ovary, uterus, testis and epididymis, prostate, skin, mammary gland, lung, heart, spleen, lymph nodes, thymus, bone marrow, bone, skeletal muscle, brain, spinal cord, nerve, eye.

Statistical Analysis

Statistical analyses were performed by an IBM 370 series computer. The computer, as programmed, first examined the data for normality using the Wilk and Shapiro W statistic and for homogeneity of variances using the Levene test. Statistical significance at P = 0.05 was based on an analysis of variance.

Results

One treated dog was sacrificed in the fifth week of the study because of poor condition (loss of appetite, vomiting, dehydration). One additional treated dog had a loss of appetite during the third week and was offered a change of diet and began to eat again. No other changes were reported.

No drug induced EKG changes were observed. Ophthalmological examination was unremarkable.

Two treated dogs showed abnormal hemograms. The dog sacrificed during the fifth week of the study had decreases in RBC, Hgb, Hct; leucocytosis, decreased platelets, and increased prothrombin time. The other dog had a decrease in WBC total and differential. No other changes occurred.

No adverse biochemical changes occurred except in the animal sacrificed during the fifth week of the study. This animal had elevated SGOT, SGPT, alkaline phosphatase, bilirubin, BUN, creatinine and K^+, and decreased glucose, total protein, albumin, Na^+ and Cl^-. T_4 values showed a significant increase in the treated animals at 4 weeks, but were comparable to the controls at 8 and 13 weeks.

No drug related urinalysis changes were evident from examination of the data.

No gross morphological changes were observed except for the dog sacrificed in poor physical condition. This dog had hemorrhage of stomach, gall bladder, left ventricle and hemoperitoneum.

Histologically, cytoplasmic vacuolation of the adrenal zona glomerulosa occurred in three treated dogs, while cellular myocardial infiltration occurred in three dogs. Thyroid follicular and bone marrow hyperplasia each occurred in one treated dog. Thyroid hyperplasia was also observed in two dogs.

Conclusion

This study was undertaken to determine whether the changes observed in absolute and relative liver weight and in absolute and relative thyroid weight observed in the previous 90 day dog feeding study were drug related. Although no adverse effect on these organs were observed in this study, DT still considers 2 mg/kg of MK-401 to be the no-effect level in the 90 day dog study.

DT's conclusion is based on the histological results reported in this 90 day study.

F. Reproduction Study in the Female Rat

Performing Laboratory:	Merck, Sharp & Dohme Research Laboratory West Point, Pa.
Species/Strain:	Rat/Charles River CD
No. of Females/Group:	14
Dose Levels:	0, 0, (control), 2, 20, 100 mg/kg
Vehicle:	0.5% methylcellulose
Route of Administration:	Oral, by gavage

Duration of Dosing: 14 days prior to mating, throughout pregnancy to day 21 post partum.

Methods:

After 14 days of drug administration (Day 0) the females were placed with untreated males of the same strain for breeding. Dosing of the females continued throughout the breeding period. Upon detection of spermatozoa in the daily vaginal lavage (day 1 of gestation) the mated females were removed, weighed and housed 4/cage. On day 14 the females were placed in individual cages. Dosing of females continued throughout gestation, parturition and to day 21 post partum. Animals were allowed to litter, with pups being counted, weighed, examined externally and sexed on days 1 and 21. Litters were culled to 8 pups on day 1 postpartum. At weaning, pups were randomly selected for continuation of a three month oral toxicity study of MK-401. All females were sacrificed after selection of offspring for 90 day oral toxicity study. The F_1 pups selected for the 14 week oral toxicity study were placed in the same dosage group as the F_0 mothers.

Observations

1. Physical appearance and behavior - daily
2. Maternal status - the following parameters were recorded during the study: maternal body weight during prebreeding, gestation and lactation; pregnancy rate, gestation time, number of implantation sites, post implantation survival rate
3. Fetal development - pup count, pup weight, sex, pup survival were taken on days 1 and 21.

Results

There were no adverse effects on maternal physical appearance or behavior due to administration of the compound. Body weight changes were not significantly different between groups. There was a significant increase in gestation length at 20 mg/kg and 100 mg/kg. The compound had no apparent effect on post implantation survival rate nor pup survival.

G. Fourteen Week Oral Toxicity Study in Rats

Performing Laboratory:	Merck Sharp & Dohme Research Laboratories West Point, Pa.
Species/Strain:	Rat/Charles River CD1
No/Sex/Dose:	25
Age at Start of Study:	4 weeks
Drug Doses:	0, 0 (control)2, 20, 100 mg/kg
Vehicle:	0.5% methylcellulose
Route of Administration:	Oral, by gavage

Methods:

The animals used in the study had been exposed to MK-401 _in utero_, and were randomly placed in the same dosage group as _their_ F_0 parents. Animals were exposed to the compound via gavage for 90 days in addition to the _in utero_ exposure.

Observations

Physical appearance:	daily
Body weight:	pretest and twice weekly
Ophthalmologic examination of Control I, and high dose animals:	Weeks 4, 8, and 13
Hematology consisting of Hgb, Hct, ESR, WBC total and differential, clotting time, platelets:	Weeks 4, 8, and 13
Biochemistry consisting of glucose, BUN, albumin, total protein, SGPT, alkaline phosphatase, Na^+, K^+, Cl	Weeks 4, 8, and 12

T_3 uptake and T_4 levels:	Days 20, 49, 84
Microscopic examination of vaginal washing in females used for thyroid function tests for correlation between estrus and thyroid function tests:	Daily for 7 days preceeding thyroid function tests
Gross postmortem examination of all animals:	At termination of the study
Organ weights of spleen, heart, kidneys, testes, liver, brain, thyroid:	At termination of the study

The following tissues were examined microscopically from 12 animals/sex of control and high dose groups at termination of the study: salivary gland, stomach, small and large intestine, liver, pancreas, adrenal, parathyroid, pituitary, thyroid, kidney, urinary bladder, ovary, uterus, skin, lung, heart, spleen, lymph node, thymus, bone marrow, bone, skeletal muscle, brain, spinal cord, nerve (sciatic) eye:

Microscopic examination of the following tissues from all rats: liver, thyroid, salivary gland (submaxillary) urinary bladder, uterus:	At termination of the study
Microscopic examination of all tissues with gross changes:	At termination of the study

Results

No treatment related toxic signs were noted. Two control rats died and one was sacrificed due to poor condition during the study. One low dose male died accidentally and one mid-dose animal was found dead. There was a significant increase in body weight in the low dose animals (male and female) over the controls after six weeks on the study. No other weight differences were observed.

No significant difference was apparent between the control and treated animals with respect to hematology, biochemistry or T_3 uptake and T_4 content. Estrus has no effect on thyroid function tests.

The following organs showed significant difference in weight when compared to the controls: thyroid, increases, both absolute and relative at the high dose in females; and as a percentage of brain weight, significant at all dose levels; spleen, relative decrease at low and mid dose in females; spleen, decrease at all dose levels in males; kidneys, relative increase at the high dose level in males.

The following histopathological lesions were observed in the study: 3 salivary gland carcinomas (2 low dose and 1 mid dose); urinary bladder hyperplasia (1 mid dose and 1 high dose); liver hyperplasia (1 high dose); endometrial sarcoma (1 mid dose).

Conclusions

Based on the thyroid weight data and the histopathology data a no effect level has not been demonstrated in this study.

H. Fourteen Week Oral Toxicity Study in the Rat

Performing Laboratory:	Merck, Sharp & Dohme Research Laboratories West Point, Pa.
Species/Strain:	Rat/Charles River CD
No/Sex/Group:	25
Age of Animals as start of study:	4 weeks
Dose levels:	0, 55 mg/kg
Vehicle:	0.5% methylcellulose

Method:

This study was performed to determine whether the toxicity observed in the previous fourteen week study was drug related or was spontaneous in origin. This study was conducted in the same manner as the previous study with examination of the same physical, hematological, biochemical, gross and microscopic tissue examinations. The parameters were examined at the same intervals as in the previous study.

Results

Several control and treated animals exhibited a subcutaneous swelling of the ventral cervical region in the 10th week of the study. This was diagnosed as infectious sialoadenitis at autopsy.

There was no adverse effect of compound administration on hematology or biochemistry tests, including thyroid function tests.

Mean absolute and relative kidney weight increased in treated females, and mean relative kidney weight increased in treated males. Mean relative liver weight decreased significantly in treated male rats.

Thyroid weights were comparable between control and treated rats.

The following histopathological lesions were seen on examination of the tissues:

Control	Treated
1 salivary gland carcinoma	-
1 salivary gland focal epithelial hyperplasia	2 salivary gland focal epithelial hyperplasia
1 splenic reticulum cell sarcoma	1 splenic reticulum cell sarcoma

Conclusion

Because the changes in thyroid and spleen weight did not occur in the present study in which MK-401 was administered as a higher dose level, DT is of the opinion that these changes might not be compound related, especially since no histopathological lesion was observed. Similarly, kidney weight increases occurred in both studies, therefore DT considers this a compound and dose related effect. Based on this the no effect level for 90 day studies in rat is 20 mg/kg.

The salivary gland carcinomas observed in the first study did not occur in this study. However focal epithelial hyperplasia of the salivary gland was observed both in control and treated groups.

However, since the data package contains rat and mouse carcinogenicity studies, DT will defer a conclusion regarding this aspect of the possible toxicity of MK-401 until all the data have been reviewed.

H. Thirteen Week Oral Toxicity Study in the Rat with In Utero Exposure

Performing Laboratory: Laboratories Merch, Sharp & Dohme - Chibret
Riom, France

Species/Strain: Rat/Charles River CD

No/Sex/Group: 20

Dose: 0, 3, 30, 100 mg/kg

Vehicle: 0.5% aqueous methylcellulose

Route: oral, by gavage

Method:

MK-401 was administered to 3 groups of female rats weighing 204-305 gram for 15 days which were then mated with untreated males of the same strain. Drug dosing continued throughout the mating period. When sperm was detected in the vaginal lavage, the animals were placed in individual cages and dosed throughout gestation until day 20 postpartum. A similar group was administered the vehicle only. The animals were allowed to litter and the pups were counted, weighed, examined externally and sexed on day 1. Pups were again weighed on day 7, 14, and 21 and sexed on day 21. F_0 females were sacrificed if they did not mate within a 5 day period or failed to deliver by day 25 of gestation.

Pups were selected randomly from each litter for a 13 week oral toxicity study. The offspring selected for the 13 week study were placed in the same treatment group as the F_0 generation.

Observations F_0:

1. Physical appearance - daily
2. Body weight - premating days -15, -7, and -1; gestation days 1, 6, 14, 16, 18, 20, 21; lactation days 2, 7, 14, 21.
3. Maternal status - the following parameters were evaluated gestation time, pregnancy rate, post implantation survival.
4. Fetal development - litter size, litter weight, sex ratio, external examination were determined at termination of this portion of the study

Observations F_1:

1. Physical appearance - daily
2. Body weight - pretest and twice weekly
3. Ophthalmologic examination on control and high dose rats: weeks 4, 7, and 11
4. Hematological determinations of Hgb, RBC, Hct, ESR, WBC total and differential, clotting time, platelets done on 10/sex/group: week 5, 8, 12
5. Biochemistry consisting of glucose, BUN, total protein, albumin, SGPT, alkaline phosphatase, Na^+, K^+, Cl^-: week 5, 8, and 12

6. Urinalysis of protein, bilirubin, glucose, blood: weeks 5, 8 and 12

7. Gross necropsy on all animals: At termination of the study

8. Organ weights of the following: brain, heart, kidney, liver, spleen, testes, thyroid: At termination of the study

Histopathology of the following was done at termination of the study:

1. All organs with gross changes
2. Salivary gland and urinary bladder from all animals
3. On 10/sex/control and high dose groups, the following organs: stomach, small intestine, large intestine, liver, pancreas, adrenal, pituitary, thyroid, parathyroid, kidney, urinary bladder, ovary, testis, epididymis, prostate, skin, lung, heart, spleen, lymph node, thymus, bone marrow (femur), bone joint, skeletal muscle, brain, spinal cord, sciatic nerve, eye with optic nerve.

Results

F_0 animals

No toxic signs and no mortality were reported. There was a decrease in weight gain during the premating and gestation periods in the low dose group, while all treated groups showed a decrease in weight gain during the gestation period. The lowest dose group rats gained least weight during the study.

Pregnancy rate, post implantation survival rate and litter size were unaffected by administration of MK-401. There was a significant increase in gestation time at the high dose level. There was a decrease in pup litter weight at the high dose level as well as a decrease in the number of pups surviving to 21 days at 3 mg/kg and 100 mg/kg.

F_1 animals

All animals survived the study except for one low dose animal which was sacrificed because of injury. Salivation occurred after dosing in high dose animals.

There was a decrease in body weight gain in females at all dose levels when compared to the controls; there was also decreased weight gain in males which was significant at the mid and high dose levels.

No treatment related ophthalmologic abnormalities were reported. No difference was seen in hematological studies between control and treated animals.

Alkaline phosphatase increased significantly in high dose males at all testing intervals. Terminal glucose values decreased significantly in high dose animals. There were no apparent treatment related urinalysis changes.

Gross morphological examination revealed no treatment related changes. Thyroid and liver weight decreased at all treatment levels, though these decreases were not significant.

Histologically, these were no thyroid abnormalities. Apart from increased mitotic activity in transitional epithelium of the urinary bladder of two high dose males, no adverse histological effects were observed.

Conclusion

Based on the changes in alkaline phosphatase and glucose levels and the histological appearance of bladder changes in the high dose males, 30 mg/kg of MK-401 is determined to be the no effect level in this study.

I. Oral Reproduction Study in the Female Rat

Performing Laboratory:	Dawson Research Corporation Orlando, Florida
Species/Strain:	Rat/Charles River COBS CD
Wt. at Start of Study:	2.5-320 grams
No. of Females/Dose:	50
Doses:	0, 0, 5, 20, 80 mg/kg

Vehicle: 0.5% methylcellulose

Route of Administration: Oral, by gavage

Duration of dosing: 14 days premating through 21 days post partum

Methods:

Two hundred and fifty adult females were treated with MK-401 or vehicle for fourteen days, then placed with an equal number of untreated males of the same strain for breeding. When spermatozoa was detected in the vaginal fluid, the females were moved to individual cages and further treated with MK-401 at the assigned dose level or with the vehicle until day 21 postpartum. Females were allowed to litter and pups were selected from the F_1 generation for a one year oral carcinogenicity study and a lifetime oral carcinogenicity study.

Observations:

Physical signs - daily

Body weight - premating days -14, -7, and 0; gestation days 1, 8, 12, 14, 16, 18, 20, 22; lactation days 2, 7, and 14

Maternal Status - The following parameters were examined at termination of the study: pregnancy rate, gestation length, post implantation survival rate.

Fetal Development - Litter size, litter weight; pup survival were recorded on the appropriate days

Results

Focal alopecia, dacryorrhea and stained groin appeared in all groups. One control and one high dose female were sacrificed during the study.

Body weight was comparable between control and treated animals. The administration of the compound had no apparent effect on pregnancy rate.

Gestation time was increased in high dose females. No adverse effect was apparent on post implantation survival rate.

There was no apparent difference between the control and treated groups relative to litter size, litter weight, sex ratio, or pup survival at day 4 or day 20 post partum.

J. Fifty Four Week Chronic Toxicity Study in Rats Following *In Utero* Exposure

Performing Laboratory:	Dawson Research Corporation Orlando, Florida
Species/Strain:	Rat/Charles River CD COBS
No. of Animals /Sex/Group:	25
Age of Animals at start of Study:	4-5 weeks
Dose Levels:	0, 0(control) 5, 20, 80 mg/kg
Vehicle:	0.5% methylcellulose
Route of Administration:	Oral, by gavage

Methods:

Pups were randomly selected from litters and assigned to the same dose levels as the F_0 generation. MK-401 was administered at the assigned dosage by gavage, once daily. Control animals received the vehicle only. Dosage was adjusted weekly on the basis of body weight. No hematology or clinical chemistry studies were performed.

Animals were sacrificed in the 53rd or 54th weeks.

Observations

Physical Signs - daily

Palpation for masses - weekly

Body Weight - Twice weekly x 3 months; weekly thereafter

Gross necropsy on all animals - At termination of the study

Microscopic examination of the following tissues of all control and high dose animals was done at termination of the study: adrenals, bone, bone marrow, brain (cerebrum, cerebellum, and medulla) and spinal cord, colon, duodenum, heart, ileum, jejunum, kidneys, liver, lungs, mesenteric lymph node, mammary gland, ovaries or testicles and epididymides, pancreas, pituitary, prostate or uterus, salivary glands, sciatic nerve, seminal vesicles, skeletal muscle, skin, spleen, stomach (glandular and non-glandular), thymus, thyroids, all tissue masses, urinary bladder, and samples of any other tissue showing macroscopic abnormality. Eyes were collected and fixed in Russell's fixative solution. All significant antemortem observations were commented on or confirmed at necropsy by a pathologist. Photographs were taken of all significant gross lesions.

Microscopic examination of all animals dying spontaneously or sacrificed due to poor condition was done at termination of the study.

Results

Physical signs of alopecia, piloerection and swollen limbs appeared in both control and treated animals with equal frequency, and were apparently unrelated to drug administration.

Body weight increases were comparable among all groups except for the low dose group in which body weights were significantly higher than in the pooled controls. Seven animals died during the course of the study, five of them from intubation accident. One middose female died of undetermined causes and one high dose female had a mammary mass.

Gross necropsy examination was unremarkable with no morphological changes in the treated animals which were not seen in the controls, or which could be attributed to administration of the compound.

Histologically, an increased incidence of the following lesions were reported in the high dose males: pancreatic acinar atrophy, chronic degeneration of the pancreas, and chronic myocardial degeneration. Bone marrow hyperplasia occurred in four high dose animals as compared with none in the control. One mid dose animal showed the condition.

The following primary neoplasms were observed in this study:

Group	Tumors seen	Time of Appearance
Control I	2 pituitary adenomas	54 weeks
Control II	1 prostate gland adenoma	53 weeks
5 mg/kg	1 uterine polyp 1 pituitary adenoma	53 weeks

20 mg/kg	1 mammary gland adenocarcinoma 1 fibrosarcoma 1 lymphoma	3 weeks
80 mg/kg	1 mammary gland adenocarcinoma	8 weeks

Conclusion:

The incidence of neoplasm in this study is very low, consequently the question of the carcinogenicity of MK-401 will probably be more readily addressed after review of the chronic carcinogenicity bioassays in the rat and mouse. Based on the other types of toxicity seen in this study, the no effect level for toxicity other than carcinogenicity is 5 mg/kg.

K. Mouse Teratology Study

Performing Laboratory:	Merck Sharpe & Dohme Research Laboratory West Point, Pa

1. Range Finding

Species/Strain:	Mouse/CF$_1$ S
No. of Females/Group:	5
Route of Administration:	Oral/Gavage
Drug Doses:	0, 25, 50, 100, 200, 400 mg/kg
Vehicle:	0.5% methylcellulose
Duration:	10 days
Weight of Animals:	22.7-37.1 gm
Observations:	Body weight determination on alternate days

Results:

No mortality or toxic signs occurred in the treated animals. There was a decrease in body weight among all treated groups. Weight loss was similar in all groups except for the lowest dose group where the weight loss was less pronounced. The dosage for the teratology study was determined on the basis of the weight loss in this range finding study.

2. Teratology Study

Species/Strain:	Mouse/CF$_1$S
No. of Females/Group:	20
Route of Administration:	Oral/Gavage
Drug Doses:	0, 0, 2, 10, 50 mg/kg
Vehicle:	0.5% methycellulose
Duration:	Day 6 - day 15 of gestation

Observations

1. Toxic signs - daily
2. Maternal body weight - recorded on day 1 of pregnancy and on alternate days 6 to 14 of gestation.
3. Reproductive status - the following parameters were evaluated at sacrifice on day 18 of gestation: pregnancy rate, number of corpora lutea, implantation sites, number of fetuses.
4. Fetal Development - mean fetal weight and sex ratio were determined at termination of the study
5. Fetal examination - External and skeletal examination were conducted on all control and high dose fetuses. Visceral examination was done on one third fetuses from control and high dose groups, and all externally malformed and dead fetuses.

Results

1. No evidence of maternal toxicity was observed. All animals survived the study.
2. No significant difference in body weight was observed between control and treated animals.
3. The pregnancy rate was decreased in the treated groups as compared to the pooled controls; 92% pregnancy occurred in the pooled controls, 80% in low and mid doses, and 75% in the high dose. There was a slight increase in the number of

resorptions at the high dose level. The number of corpora lutea and implantation were comparable among control and treated animals.

Fetal Development:

The sex ratio was comparable between litters from control and treated females, except for the middose group which showed a higher ratio of males/females. Mean litter weight was significantly decreased in the high dose group.

Fetal Examination:

Skeletal abnormalities reported in offspring from both control and treated animals were: mishapen atlas, unossified sternebrae, presence of 14th rib, trace ribs, and misaligned sternebrae. There were no visceral abnormalities except in one offspring from the 10 mg/kg treatment group, which showed several soft tissue alterations. There was a increased incidence of postaxial pseudopolydactyly of both forepaws in the mid and high dose groups.

Conclusion

Based on the increased incidence of pseudopolydachyly of both forepaws occurring at the mid and high dose levels, DT has determined that the no effect level for this study is 2 mg/kg.

L. Teratogenic Evaluation in the Rabbit

Performing Laboratory:	Merck, Sharp & Dohme Research Laboratory West Point, Pa.

1. Range Finding

Species/Strain:	Rabbit/New Zealand
Weight of Animals:	3780-5170 grams
No. of Females/Group:	4
Drug Doses:	0, 25, 50, 100, 200, 400 mg/kg
Vehicle:	0.5% methylcellulose

Route: Oral/Stomach tube

Duration: 9 days

Observations

Body weights recorded on days 1, 3, 5, 6, 9 of dosing. Terminal body weight taken on day 10

Results

Mean body weight loss occurred at dosage levels of 100 mg/kg and higher of MK-401. Food and water intake decreased in the high dose animals. No deaths occurred in the study. Based on this study the high dose for teratological evaluation was set at 50 mg/kg.

2. Teratological Evaluation:

Species/Strain: Rabbit/New Zealand

No. of Females/Group: 15

Doses: 0, 0, 2, 10, 50 mg/kg

Vehicle: 0.5% methylcellulose

Duration of Dosing: Day 7-day 15 of pregnancy

Pretreatment: 25 i.u. HCG on day zero of gestation

Observations

1. Maternal body weight - recorded on days 0, 7, 9, 11, 13, 15, 17 and 28 of gestation
2. Reproductive status - the following parameters were evaluated at sacrifice on day 28 of gestation: pregnancy rate, number of corpora lutea, total number of fetuses.
3. Fetal development - mean fetal weight and sex ratio were determined at termination of the study.
4. Fetal examination - External and skeletal examination were conducted on all fetuses. Visceral examination was conducted on all fetuses from both control and the high dose group, and on all externally malformed and dead fetuses from the low and mid dose groups.

Results

1. One low dose female died from an intubation accident on day 19 of gestation. No other mortality occurred. Maternal body weight was significantly decreased in the mid and high dose animals during drug administration (gestation days 7-15). Several animals aborted during the pregnancy, but the abortions were evenly distributed among the control and treated animals. One control animal died during the study.

2. There were no significant changes in pregnancy rate, corpora lutea or implantation sites among the control or treated animals. There was a slight increase in the number of resorptions among the treated animals, with the lowest dose animals having the highest total number of resorptions. There was a slight increase in the number of dead fetuses at the high dose level.

3. Mean fetal weight was slightly decreased at the high dose level. There was a slight increase in the ratio of males/females at the high dose level.

4. Only four fetuses were reported to have external malformations: 3 control and one middose. Skeletal malformations occurred to an equal extent in control and high dose animals. There was no significant difference in visceral abnormalities between the high dose fetuses and those of the pooled controls.

Conclusion

Based on the results reported in this study, MK-401 is not teratogenic in the rabbit. The no-effect level is 50 mg/kg.

M. Lifetime Oral Carcinogenicity Study in Mice

Performing Laboratory: Dawson Research Corporation
Orlando, Florida

1. Nine Week Pilot Study to Determine Dose Levels For the Carcinogenicity Study

Species/Strain: Mouse/Charles River CD-1

No. of Animals/Sex/ Group:	**20**
Age at Start of Study:	**42 days**
Doses:	**0, 50, 100, 150, 200, 250 mg/kg x 14 days** **0, 50, 100, 500, 750, 1000 mg/kg x 7 weeks**
Vehicle:	**0.5% methylcellulose**
Route of Administration:	**Oral, by gavage**

Methods:

Mice were randomly assigned to six groups of 10 males and 10 females. Five groups received the compound at levels of 50, 100, 150, 200 and 250 mg/kg daily for 14 days, when the dosage level of those rats receiving 100, 150, and 200 mg/kg/day was increased to 500, 750, and 1000 mg/kg/day respectively. Doses of 50 mg/kg and 250 mg/kg were retained. The new dosage levels were administered for the remainder of the study.

Observations:

Body weight - pretest and twice weekly

Mortality - twice daily

Physical signs - daily

Compound related effects - 1, 2, 4, hours post dosing on days 2-6, and days 15-20

Results:

Six animals died of intubation accidents prior to dosage increase. Three additional animals (dose level not reported) died of undetermined causes. Of twelve animals which died after dosage was increased, eight deaths were reported to be from intubation accidents or respiratory disease; the cause of death in the others could not be determined. One of these with undetermined cause of death was a control animal; three were high dose. Clinical signs preceeding death were reduced activity, tremors and decreased body

temperature, regardless of the cause of death. The company states that the dose levels selected for the lifetime oral mouse carcinogenicity study were based on the unexplained death of the animals at the 1000 mg/kg dose.

2. Lifetime Oral Carcinogenicity Study in Mice

Species/Strain:	Mice/Charles River CD-1
No. of Animals/Sex/ Dose:	50
Age at Start of Study:	4-5 weeks
Weight:	19-36 grams
Doses:	0, 0, 0(control) 50, 150, 450 mg/kg
Vehicle:	0.5% aqueous methylcellulose
Route of Administration:	Oral intubation
Duration of Dosing:	92-121 weeks

Methods:

Three groups of Charles River CD$_1$ mice, each containing 50 males and 50 females were intubated daily with 50, 150 or 450 mg/kg of MK-401 for 92-121 weeks. Doses were adjusted according to the most recent body weight.

Three additional groups of 50 males and 50 females each were used as controls and were administered the vehicle only, 0.6% methylcellulose. Samples of the compound were analysed for identity, strength, quality, and purity prior to start of the study and at weeks 1, 34, 58, 61, 75, 94 and at study termination.

Drug dosing mixtures from weeks 77, 82, 86, 91, 98, 104, 112 and 118 were analysed for MK-401 content.

The study was terminated according to the following schedule:

High Dose Males	11/20 - 11/21/79	Week 92
Low Dose Males	11/26 - 11/27/79	Week 93
Middle Dose Males	12/10 - 12/11/79	Week 95
Low Dose Females	5/15/80	Week 118
Middle and High Dose Females	6/9 - 6/11/80	Week 121

Observations:

Physical signs - daily

Mortality - Twice daily

Physical examination for tissue masses - weekly

Body weight - Twice weekly for 3 weeks, weekly thereafter

Blood and bone marrow smears - at termination of the study

Drug blood level determination on 5/sex/group - One hour post dosing at study termination

Gross necropsy of all animals - at termination of the study

Histological examination of the following organs of all Control I and all high dose animals were done at termination of the study: adrenals, brain (cerebellum, cerebrum, medulla) and spinal cord, colon, duodenum, eyes (fixed in Russell's fixative), heart, ileum, jejunum, kidneys, liver and gallbladder, lung, lymph node (mesenteric), mammary gland, ovaries, pancreas, pituitary, prostate, salivary gland, sciatic nerve, seminal vesicles, skeletal muscle, skin, spleen, stomach (glandular and non glandular), testes and epididymides, thymus, thyroids (including parathyroid), tissue masses and suspected tumors, urinary bladder, uterus. Bone and bone marrow were also collected. Photographs were taken of all significant gross lesions.

Histological examination of the urinary bladder of all animals and all tissues with gross changes was done at termination of the study.

Results

No physical signs attributable to treatment were reported. Inactivity, loss of balance, dyspnea occurred as terminal changes prior to death and was seen in control and treated animals.

Several animals (all Control I) died early in the study from intubation accidents. They were replaced on day 7 of the study. Except for the mid dose females where weight gain was significantly decreased, there were no variations in weight gain been the control and treated animals. A number of male mice developed preputial abscesses or ear infections characterized by alopecia and a moist exudate. Cultures from abscess and exudates were examined by State Lab in Kissimore, Florida and diagnosed as leucolytic streptococcus and coagulase positive staphylococcus respectively. Lesious were treated with Achromycin Antibiotic Ointment 3%.

Hematology values were not significantly different between the control and treated animals.

Samples of the compound dosing suspension taken after dosing 30%, 60% and 90% of animals at each dose level, yielded means of 88 ± 18.6%, 80 ± 20.5% and 68 ± 27.8% of the 50 mg/kg, 150 mg/kg and 450 mg/kg doses respectively. Thus the actual doses administered to mice in this study were 44 ± 9.3 mg/kg; 120 ± 30 mg/kg, and 306 ± 124 mg/kg respectively.

Of the tissues examined histologically, there was no difference between any of the control groups and the treated animals with respect to the number of animals necropsied with neoplasms or with malignant neoplasms. No significant difference could be observed between the control and treated animals with respect to tumor types. No other histopathological lesions were reported in the treated animals which did not occur with equal frequency in the control animals.

Conclusion

Based on the data presented in this study, DT is of the opinion that MK-401 is not carcinogenic in mice.

The no effect level for this study is 306 mg/kg.

No salivary gland or urinary bladder tumors were observed in this study.

3. Lifetime Oral Carcinogenicity Study in Rats following In Utero Exposure

Performing Laboratory: Dawson Research Corporation
Orlando, Florida

Species/Strain: Rat/Charles River CD

No/Sex/Dose: 50

Age at Start of Study: 4-5 weeks

Weight: 77-148 grams

Doses: 0, 0, 0(control), 5, 20, 80 mg/kg

Vehicle: 0.5% aqueous methylcellulose

Duration of Study: 29 months

Method:

Rats selected for this study were progeny from an Oral Reproduction Study in Female Rats conducted by Dawson Research Corporation and reported earlier. The pups were randomly selected within each dosage group for a total of 50 males and 50 females per group. The test compound was administered by gavage for a total of 848-852 doses to males and 869-877 doses to females. Control animals were subjected to the same regimen except that they were administered 0.5% aqueous methylcellulose instead of the test compound.

Samples of the compound were analysed for MK-401 content and based on the analysis the amount administered to the animals was calculated to be:

Intended Dose Level mg/kg/day	Actual Dose Level mg/kg/day
5	3.8
20	12.6
80	48.8

Observations:

Physical signs - daily

Mortality - Twice daily

Palpation for tissue masses - weekly

Body weight - weekly thereafter

On 10/sex/group, hematology consisting of the following: RBC, Hgb, Hct, ESR, MCV, MCH, MCHC, platelet, WBC total and differential, clotting time: At 3, 6, 9, 12, 18 and 24 months

On 10/sex/group, biochemistry of the following: glucose, BUN, protein, albumin, SGPT, alkaline phosphatase, Na$^+$, K$^+$ and Cl$^-$: Same intervals as hematology

Ophthalmological examination of all animals in control and high dose groups: At 6, 12, and 24 months

Gross necropsy of all animals was done at termination of the study.

The following organs were weighed from all animals sacrificed at termination of the study: brain, heart, kidney, liver, thyroid

Histological examination of all gross lesions and all tumors was done at termination of the study.

Histological examinaton of the following tissues from all control and high dose animals was done at termination of the study: adrenals, bone, bone marrow, brain (cerebrum, cerebellum, and medulla), and spinal cord, colon, duodenum, heart, ileum, jejunum, kidneys, liver, lungs, mesenteric lymph node, mammary gland, ovaries or testicles and epididymides, pancreas, pituitary, prostate or uterus, salivary glands, sciatic nerve, seminal vesicles, skeletal muscle, skin, spleen, stomach (glandular and non-glandular), thymus, thyroids with parathyroid, all tissue masses, urinary bladder, and samples of any other tissue showing macroscopic abnormality.

Results

There were no observable differences in body weight changes between the control and treated animals. Ophthalmologic examination was unremarkable.

There was increased staining of abdominal hair in the high dose males and females as compared to the controls. No other physical signs occurred in the treated animals which were not observed in the controls.

The mortality rate was comparable among all treatment and control groups.

Hematology values were similar in control and treated animals. No drug related biochemical changes were reported.

Middose females showed significant increases in organ/brain ratio with respect to liver weight, and high dose males showed the same effect with respect to thyroid weight. Examination of individual organ weights revealed that the differences were due in both cases to one animal which had an extremely large liver and thyroid gland respectively, thus no biological significance is attached to these data.

With respect to histopathology, the incidence of kidney tubular adenoma combined with adenocarcinoma is higher in the high dose males than in the pooled controls, and the data for the other treated groups was not submitted. The other type of toxicity apparent in this study is the increase in kidney epithelial hyperplasia in female rats. This is significantly higher in the mid and high dose groups than in the controls. The bone marrow hyperplasia reported in the 54 week toxicity study, and the salivary gland carcinomas and urinary bladder hyperplasia reported in earlier studies are not apparent in this study.

Conclusion

The only cause of carcinogenic concern in the two year oral rat study is the incidence of combined kidney tubular adenomas and adenocarcinomas in the high dose male rats. Other toxicological concern centers on the hyperplasia of kidney epithelial tissue in the female rats at the mid and high dose level. Two 90 day oral studies reported previously have shown increases in relative kidney weight in males at 55 mg/kg and 100 mg/kg of MK-401; and mean absolute and relative kidney weight increases in females at >55 mg/kg.

Based on these histopathology data, DT is requesting a histological examination of all the kidney tissues in the other dosage groups as well as the other control groups in this study. DT also requests any historical data on the incidence of this tumor type in their control rats of this strain.

Until these data have been supplied, the toxicological evaluation of MK-401 remains incomplete.

When the requested data have been submitted, if the compound is positive for carcinogenicity, a safe use level will be calculated using appropriate statistical methods. If the data allays DT's concern for possible carcinogenicity, a tolerance will be calculated using data from the most sensitive study in the data package.

Based on the company's dosage calculations in the two year rat and mouse studies, the company should be aware that the actual dose levels administered to the animals in all the gavage studies in this submission might in every case be lower than the stated doses. This will affect the no-effect levels and subsequently the tolerance.

Summary

DT has reviewed the toxicological data in support of MK-401, and had assigned the following no effect levels for the relevant studies. The other studies in the data package were either range finding studies or were too limited in duration to be used in calculating the tolerance for MK-401

1. Fourteen Week Oral Toxicity Study in Dogs:
   2 mg/kg

2. Fourteen Week Oral Toxicity Study in Rat:
   n.e.l. not demonstrated

3. Fourteen Week Oral Toxicity Study in the Rat:
   20 mg/kg

4. Thirteen Week Oral Toxicity Study in the Rat with *in utero* exposure:
   30 mg/kg

5. Fifty Four Week Chronic Toxicity Study in Rats following *in utero* exposure:
   5 mg/kg

6. Mouse Teratology Study:
   2 mg/kg

7. Teratogenic Evaluation in the Rabbit:
   50 mg/kg

8. Lifetime Oral Carcinogenicity Study in Mice:
   450 mg/kg intended dose
   306 mg/kg actual dose

9. Lifetime Oral Carcinogenicity Study in Rats following *in utero* exposure

Additional data on kidney tumors requested

The company should be informed that:

1. Because of the compound's apparent lack of solubility, and the discrepancy between the intended dose and the actual dose administered in the two chronic studies, the company should determine the actual dose levels administered in the relevant studies.

2. The company is requested to submit the histology data for kidney tissues in treated groups other than the high dose males, as well as for the other control groups in the study. DT also requests any historical data on the incidence of kidney tubular adenomas and adenocarcinomas on control rats of this strain in their laboratory.

3. Pending the receipt and review of this information, DT can only recommend a 90 day withdrawal time for MK-401. This is based on available toxicology and residue depletion data and a tentative tolerance of 10 ppb.

Joycelyn E Stewart
Joycelyn E. Stewart, Ph.D.

Judith W. Hausewich 10/13/82
Group Leader

DCH CONCURRENCE

cc:
HFV-300
HFV-330
HFV-340
HFV-16(3)

JEStewart:crj:0961A
DRAFT:9/7/82:REDRAFTED:9/30/82:FINAL:10/6/82

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service HFV-185

Memorandum

Date October 5, 1983

9/17/84

From Toxicology Staff, HFF-[illegible]

Subject [illegible] MK-401 - Life-Time Carcinogenicity Studies in Rats Following *in utero* Exposure

To Consumer Safety Staff, HFV-[illegible]

Merck Sharp and Dohme
Research Laboratories
P.O. Box 2000
Rahway, NJ 07065

This memorandum is in reference to the sponsor's submission dated January 21, 1983 and the Toxicology Staff memorandum dated May 16, 1983 concerning the "Life-Time Carcinogenicity Study in Rats Following *in utero* Exposure". TS expressed concerns over the incidence of kidney tumors in the high dose (48.8/kg/day) male rats and the hyperplasia seen in the kidney epithelial tissue of female rats. On the basis of the guidelines outlined for the submission of a protocol for the CAC/BVM evaluation of carcinogenicity studies, "MK-401-Life-Time Carcinogenicity Study in Rats Following *in utero* Exposure" was presented by the Toxicology Staff (reviewer and group leader) to Dr. Theodore Farber and Dr. Lawrence Valcovic to confirm these suggestive findings. The following data summary of kidney tumors and other effects observed by the sponsor in the life-time carcinogenicity study in rats were discussed on September 15, 1983.

Performing Laboratory: Dawson Research Corporation, Orlando, Florida.
Species/Strain: Rat/Charles River-CD-COBS.
No. of Animals/Sex/Group: 50.
Dose Levels: Intended - 0, 0 (control), 5, 20, 80 mg/kg.
Actual - 0.0 (control), 3.9, 12.6, 48.8 mg/kg.
Vehicle: 0.5% methylcellulose suspension
Route of Administration: Oral, by gavage.

Length of Exposure: 14 days prior to breeding, through gestation and lactation and later for 122 weeks (males) and 125-126 weeks (females), total duration of study was 29 months.

Observations: Individual and mean body weight, physical signs, hematology, serum biochemistry, animals dead or sacrificed with primary neoplasms, time of onset of confirmed neoplasms, histomorphology.

Results:

1. Treatment with MK-401 had no significant effect on body weight.

2. No ophthalmologic effects were attributed to drug treatment.

3. Some of the clinical signs such as facial staining, alopecia, swollen eyelids, swollen ears and feet, ulcerations, piloerection, dacryorrhea, inactivity, loss of balance, labored breathing, preputial discharge and swelling were observed in both treated and control rats and were not considered to be treatment related.

Lower abdominal hair staining was observed in both male and female rats treated with the high-dose as well as with the mid-dose in male rats only.

4. The incidence of mortality was approximately twice that of control in the high dose treated male animals at 18 and 24 months of age. The sponsor concluded that treatment with MK-801 had no apparent effect on the incidence of mortality based on the low incidence of deaths observed during the 12 to 18 month period and the overall mortality at the time of termination of the study. No explanation was provided for the significantly higher mortality observed during the 18 to 24 month period of the study.

5. The periodical clinical hematology and serum biochemical analyses showed no treatment-related changes.

6. The sponsor claimed that histomorphological examination showed no increased incidence of benign or malignant neoplasia in drug treated rats and acknowledged only a significant increasing trend in the incidence of kidney pelvic epithelial cell hyperplasia in female rats at 20 and 80 mg/kg dose levels. Furthermore, the sponsor considered this effect as secondary to the pelvic lesions such as pyelitis of infectious origin, pelvic calculi, and pelvic mineralization. However, review of the histopathological data by DT (October 6, 1982) found that the incidence of kidney tubular adenoma together with adenocarcinoma was higher in the high dose males than in the pooled controls, and that there was an apparent increase in kidney epithelial hyperplasia in female rats at the mid and high dose levels. The bone marrow hyperplasia, salivary gland carcinomas and the urinary bladder hyperplasia reported in the 54-week rat toxicity study were not apparent in the present study.

The sponsor submitted the historical control data from the performing laboratory and from their own laboratory on the incidence of tubular adenoma and adenocarcinoma in the same rat strain used in these studies and argued that the incidence of these tumors was not significant. Furthermore, the sponsor also argued that the hyperplasia of the kidney epithelial tissue in female rats is secondary to other accompanying renal pelvic changes commonly seen in rats at that age, and therefore, is not drug-related. Rereview of the life-time carcinogenicity study in rats following *in utero* exposure of MK-401 confirms the previous concerns expressed by DT (review dated October 6, 1982). The historical control data was presented for the CAC review. The following tables derived from the sponsor's data on the incidence of kidney tumors were included for the information of the CAC.

Summary of kidney tumors and other effects - Life-Time Carcinogenicity Study in Rats following *in utero* Exposure to MK-401

Female Rats

				mg/kg/day(actual)		
Tumor type/groups	0	0	0	5(3.8)	20(12.8)	80(65.8)
Tubular adenoma	1/50	1/49	0/50	0/50	0/50	0/50
Tubular adenocarcinoma	1/50	0/49	0/50	0/50	0/50	0/50
Pelvic epithelium hyperpalsia	2/50	3/49	2/50	1/50	8/50	9/50
Hydronephrosis	2/50	3/49	3/50	2/50	6/50	7/50

Summary of Kidney Tumors and other effects - Life-Time Carcinogenicity Study in Rats following *in utero* Exposure to MK-401.

Male rats

				mg/kg/day (actual)		
Tumor type/groups	0	0	0	5(3.8)	20(12.8)	80(49.8)
Tubular adenoma	1/50	1/5	0/50	1/50	0/50	3/50
Tubular adenocarcinoma	1/50	0/50	0/50	0/50	0/50	1/50
Pelvic-transitional cell carcinoma	0/50	0/50	0/50	0/50	0/50	1/50
Pelvic-epithelial hyperplasia	7/50	3/51	3/50	5/50	10/50	4/50
Pelvic-squamous cell metaplasia	0/50	0/51	0/50	0/50	0/50	2/50
Hydronephrosis	1/50	2/51	2/50	4/50	3/50	9/50

Methods of Statistical Analysis Used

The firm used the Mantel-Haenszel procedure which compares the entire life-table adjusted curves for the high dose and control groups, taking into account time to tumor and time to death without tumor. This was done for individual palpable tumor occurrences and the results cumulated over time. Results for tumor sites with fewer than 6 animals with tumors were evaluated using an exact procedure and adjustments to the P-values were made for the multiplicity of tumor sites examined. The results for kidney epithelial hyperplasia were evaluated by a trend test that measures the progressiveness of hyperplasias with increase in dose (including the controls = zero dose). Adjustments were made for multiplicity of comparisons of individual doses with controls.

CONCLUSIONS:

1) Female Rats -

There was a statistically significant trend for progressiveness of kidney epithelial hyperplasia with an increase in dose. Individual dose comparisons vs. controls showed statistically significant increases for the mid-dose group (20 mg/kg/day) (p=0.013) and for the high dose group (80 mg/kg/day) (P=0.011).

2) Male Rats - The comparison of controls vs. the high dose group showed that the occurrence of kidney tubular adenoma was statistically significant. No statistically significant evidence of an increase in kidney epithelial hyperplasia was observed except for the mid dose group (P=0.015). The firm claims that this may be a fortuitous result, since there was no evidence of a trend.

It was concluded in the meeting of September 15, 1983 that:

1. The criteria for study performance and data reporting were fulfilled by the sponsor.

2. The committee agreed with the firm's contention that the occurrence of kidney tubular adenoma observed in the high dose group was not drug-treatment-related and such rare tumors are commonly observed in aging rats. The historical control data submitted by the sponsor (letter dated January 21, 1983) and the data available in open literature in the test species supports the claim of the sponsor. Therefore, it was concluded that MK-401 is not carcinogenic in rats upon oral administration.

3. The significant incidence in male rats of kidney epithelial hyperplasia at the mid dose level and hydronephrosis at the high dose level was also discussed at the meeting and it was agreed

that these lesions were not pre-neoplastic but were considered as MK-401 treatment-related. The incidence of kidney epithelial hyperplasia observed at the mid and high dose levels in female and at the mid dose level in male rats was clearly above the control groups. Therefore, they were considered drug-related non-neoplastic lesions.

Based upon the concerns over the incidence of kidney epithelial hyperplasia and hydronephrosis, observed at the mid and high dose levels, the no effect level for the Study "Life-Time Carcinogenicity Study in Rats Following in utero Exposure", is 3.8 mg/kg/day.

Different no effect levels were set for the various submitted studies in TS memorandum dated May 16, 1983 and are summarized below to establish the safe concentration of residues for MK-401 use as a cattle fasciclicide.

Name of Study	No Effect Level (mg/kg/day)
1. 14-Week Oral Toxicity Studies in Dogs	8
2. 13 and 14-Week Oral Toxicity Studies in Rats	300
3. 54-Week Chronic Toxicity in Rats	48.8
4. Mouse Teratology Study	10
5. Teratological Evaluation in Rabbits	50
6. Life-Time Oral Carcinogenicity in Mice	306
7. Life-Time Oral Carcinogenicity Study in Rats following in utero Exposure	3.8

The agency calculates the safe concentration from the results of the most sensitive study in the most sensitive species. After evaluation of the no effect levels set for various studies, the 14-Week dog study is selected as the most appropriate to calculate the safe concentration for MK-401. The life-time carcinogenicity study in rats had a lower no-effect level, however, a 100-fold safety factor would be used for calculating the safe concentration. A thousand-fold safety factor would be used for the 14-Week dog study since,

1) a chronic dog study was not performed on MK-401

and 2) the problem of dosing encountered in the chronic rat and mouse study ~~were~~ was not detected in earlier studies, such as this particular one.

Therefore, from the 14-Week dog study the ADI is calculated on the highest dose (8 mg/kg/day) showing no observed effect or the no effect level (NEL) divided by the safety factor (1000).

$$ADI = \frac{8\ mg/kg/day}{1000} = 0.008\ mg/kg\ of\ body\ weight/day$$

The safe concentration is calculated from the acceptable daily intake (ADI), the weight in kg of an average adult human (60 kg), the amount of the product eaten per day, and the food consumption factor for the edible product. The formula used to calculate the tolerance is:

$$\text{Tolerance} = \frac{\text{ADI } (\mu g/kg/day) \times 60\ kg}{\text{Food Factor} \times 500\ g/day}$$

Therefore, the tolerance for MK-401 using the 14-Week dog study will be:

$$\text{Tolerance} = \frac{8\ \mu g/kg/day \times 60\ kg}{1 \times 500\ g/day} = \frac{480\ \mu g/person}{500\ g/day} = 0.96\ ppm$$

Thus, using the relative consumption factors, TS assigns a safe concentration for MK-401 in beef muscle of 1 ppm, liver, 2 ppm, kidney, 3 ppm and fat, 4 ppm.

Transmittal Section:

The agency has previously reviewed your submission dated January 21, 1983 and the response to that submission was communicated on May 26, 1983. Since then, we have further reviewed the life-time carcinogenicity study in rats following *in utero* exposure with special reference to the significance of the occurrence of kidney tumors and other effects observed in male and female rats at the mid and high dose levels. The agency has concluded:

1. We agree with you that the occurrence of kidney tubular adenoma observed in males of the high dose group was not related to drug-treatment and such rare tumors are commonly observed in aging rats. This decision was made based on the review of data available in the open literature and the historical control data submitted by you (letter dated January 21, 1983). Therefore, we conclude that MK-401 is not carcinogenic in rats upon oral administration based on the data made available by you for the agency's review.

2. We feel that the significant incidence of kidney epithelial hyperplasia seen at the mid dose level in male rats was related to the drug treatment. We are also concerned about the significant incidence of hydronephrosis observed in male rats at the high dose levels. The incidence of kidney epithelial hyperplasia observed at the mid and high dose levels in female and at the mid dose level in male rats was clearly above the

control groups. Therefore, they were considered drug-related non-neoplastic lesions. Based upon these concerns, we have set the no effect level of 3.8 mg/kg/day for "MK-401-Life-Time Carcinogenicity Study in Rats following in utero Exposure". We have decided to choose the actual dose level (3.8 mg/kg/day) rather than the intended dose level (5 mg/kg/day) because of the problem of dosing as reported by you in the conduct of chronic studies (rats and mice).

3. After considering the no effect levels set by the agency for all the short-term as well as chronic studies (memorandum dated May 26, 1983) the agency has chosen 8 mg/kg/day as the no effect level set for 14-week oral toxicity studies in the dog to establish the safe concentration of MK-401 residues in edible cattle tissues. The life-time carcinogenicity study in rats had a lower no effect level, however, a 100-fold safety factor would be used for calculating the safe concentration from this study. A thousand-fold safety factor would be used for the 14 week dog study since,

1) A chronic dog study was not performed on MK-401; and

2) The problems of dosing encountered in the chronic rat and mouse study were not detected in earlier studies, including this particular study.

Thus, based upon the 8 mg/kg/day dose as the no effect level, using 1000-fold as the safety factor and 500 g of daily muscle consumption, our calculations show 0.96 ppm (or 1.0 ppm) as the safe concentration for MK-401 in muscle. Using appropriate consumption factors for cattle this would calculate to 2.0 ppm in liver, 3.0 ppm in kidney and 4.0 ppm in fat.

B.R. Sonawane 10/5/83

B.R. Sonawane, Ph.D.

Judith D. Hawsworth

Group Leader

cc: HFV-16(2)
HFV-300
HFV-320(2)
HFV-220(3)
HFV-340

R/D:9-26-83:TLC:BRSonawane
F/T:10-5-83:TLC:BRSonawane

DEPARTMENT OF HEALTH [illegible]

Memorandum

File

Date December 14, 1981

From Acting Director, BVM, HFV-1

Subject Significant Events, December 7, 1981 to December 11, 1981

To Dr. Moy, HFJ-20

Gentian Violet

As the result of an adverse decision in Marshall Minerals v. FDA, which the agency decided not to appeal, a new interim policy has been articulated by the Bureau with respect to the use of gentian violet in feed. The interim policy will remain in effect until the results of the safety study underway at the NCTR have been completed and evaluated. If the results of the studies, expected to be completed in about two years, confirms the agency's suspected safety problems, the interim policy will be immediately terminated.

While it remains the agency position that gentian violet is not generally recognized as safe for any use, we will not take regulatory action against the use of gentian violet in poultry feed indicated as a mold inhibitor. This policy is intended to treat all manufacturers equally in light of the decision in the Marshall Minerals seizure case. The industry at large is being notified of this decision (letters, publicity, proposed FEDERAL REGISTER notice). This decision does not authorize any other use of gentian violet in animal feeds or drinking water.

Gerald B. Guest

Gerald B. Guest, DVM

cc: Dr. Harvey, HFV-2
Dr. Bixler, HFV-5
Ms. Sink, HFV-10
Dr. Baldwin, HFV-100
Dr. Crandall, HFV-200
Dr. Settepani, HFV-300
✓Dr. Norcross, HFV-500

Please file

MEMORANDUM OF CONFERENCE

Purpose: Meeting of the Cancer Assessment Committee

Subject: Gentian Violet

Place: Center for Veterinary Medicine/HFS Conference
Room 8-82, Parklawn Building, Rockville, MD 20857

Date and Time: November 20, 1984
2:00 pm

Participants

CAC Members

Dr. T. M. Farber, Chairman, Division of Drug & Environmental Toxicology, HFV-150 T.M. Farber

*Dr. R. C. Livingston, Division of Manufacturing & Residue Chemistry, HFV-140 ________

Dr. J. Colaianne, Division of Biometrics & Production Drugs, HFV-124 J.J. Colaianne

Dr. R. Furrow, Deputy Director, Division of Veterinary Medical Research, HFV-501 Robert Furrow

Dr. B. R. Sonawane, Executive Secretary, CAC/CVM, Division of Drug & Environmental Toxicology, HFV-156 BRSonawane

*Dr. Livingston was not present.

Others

Dr. M. Arcos, Division of Drug & Environmental Toxicology, HFV-156

Dr. R. W. Benson, Policy Development & Quality Control Staff, HFV-102

Ms. M. T. Roper, Division of Biometrics & Production Drugs, HFV-124

Dr. R. E. Osterberg, Division of Drug & Environment Toxicology, HFV-154

The meeting of the Cancer Assessment Committee of the Center for Veterinary Medicine was held on November 20, 1984 to discuss the NCTR (National Center for Toxicological Research, Jefferson, Arkansas) Technical Report, Experiment #304, September 1984. "Chronic Toxicity and Carcinogenicity Studies of Gentian Violet in Mice" and the summary of the report prepared by Dr. Martha Arcos, HFV-156 (memorandum dated November 13, 1984 addressed to Dr. Norcross, HFV-100).

Dr. Arcos briefly presented the analysis of the GLP report and pointed out the problems observed by the GLP investigators concerning the conduct of the two-year chronic Mouse Feeding Study with Gentian Violet. Some of the issues concerning the study (E304) were restated as described in the memorandum dated April 26, 1984 concerning the review of the GLP inspection report at NCTR (January 13 and March 2, 1984). Dr. Arcos also briefly presented the Toxicological Evaluation of the Gentian Violet Two-Year Chronic Mouse Study from the memorandum dated November 13, 1984 (the copy attached). She concluded that:

Chronic long-term feeding of Gentian Violet caused a significant dose-related increase in the incidence of liver tumors both in the female and male mice.

In females, the most significant observation was the dose-related increase in the incidence of liver tumors, both benign (4, 9, 39, and 21%) and malignant (4, 5, 32, and 77%) when compared to the controls for the 0, 100, 300 and 600 ppm dose levels, respectively. The similar statistically significant positive trends were observed for mortality due to the lesions, prevalence and time to onset of tumors. Furthermore, other dose-related lesions were noted for erythropoiesis of the spleen, atrophy of the ovary, reticulum cell sarcoma (type A) of the uterus; vagina, ovary and bladder, as well as ademona of the Harderian gland.

In the males, the incidence of liver tumors was 15, 17, 18, and 35% for the 0, 100, 300, and 600 ppm dose groups, respectively. Positive trends for prevalence and time of onset of tumors were observed only for malignant liver tumors in the 600 ppm dose group and for the combination of benign-malignant tumors in the 300 ppm dose group. The mortality was of borderline significance ($p = 0.02$) for the males in the 600 ppm dose group.

Other lesions observed in the males were adenoma of the Harderian gland (4, 7, 11, and 10%) and the erythropoiesis of the spleen (3.8, 14.1, 10.4, and 12%) for the control and the 100, 300, and 600 ppm dose groups, respectively. The other reproductive organs in the male mice were examined but no significant effects of any toxicological concern were noted according to telephone inquiry made to Dr. Littlefield, Principal Investigator for the Gentian Violet Study.

The Cancer Assessment Committee discussed a number of issues concerning the GLP deficiencies and their impact on the validity and the acceptance of Gentian Violet studies conducted at the NCTR. The following documents were made available for the discussion of the CAC:

- o NCTR Technical Report - Experiment 304, September 1984 entitled "Chronic Toxicity and Carcinogenicity Studies of Gentian Violet in Mice".
- o Dr. Richard H. Teske's memoranda dated December 19, 1983 and April 26, 1984.
- o Dr. Nicholas E. Weber's memorandum dated May 4, 1984.
- o Dr. Martha Arcos's memorandum dated April 26, 1984.

o Dr. Lawrence R. Volcovic's memorandum dated December 8, 1983.

The Committee discussed some of the following deficiencies considered to be significant in relation to the Gentian Violet studies which were identified during the subject GLP inspections:

o Raw data recorded in pencil

o Missing mice

o Inadequate controls in diet preparation

It was concluded that none of the noted discrepancies, errors or minor protocol or SOP deviations were found to compromise the committee's ability to determine the carcinogenic potential of Gentian Violet in mice (E304). The committee, therefore, determined that the scientific validity of the data is acceptable and judgment could be made on the carcinogenic potential of Gentian Violet.

Dr. Farber raised the question concerning the appropriateness of the statistical methods used in the interpretation of the data generated in the Gentian Violet - Two Year Chronic Mouse Study (E304). Dr. Colaianne briefly reviewed the statistical methods and stated that appropriate statistical methods and procedures have been applied in the analysis of the data. He had discussed the problem with Dr. Gaylor from NCTR and agrees with his interpretation of the data. With respect to the Bonferoni adjustments for multiple comparisons there exist a considerable controversy over the validity of these adjustments in long-term bioassay evaluations, therefore, on the recommendation of Dr. Colaianne, they were not considered by the CAC as used by the NCTR for the interpretation of Reticulum Cell Sarcoma (RCS) in reproductive organs of female mice (NCTR report Experiment 304, Table 5, page 11).

The committee unanimously agreed and concluded that the lifespan feeding study of Gentian Violet in the diet of both sexes of mice (B6C3F1) demonstrated a significant dose-related increase in the incidence of liver tumors. The female mice appeared to be more susceptible to the carcinogenic effect of Gentian Violet as substantiated by the observed increased incidence of reproductive tract and bladder reticular cell sarcoma (Type A) in the treated over the control animals. The increased incidence of these tumors (biologically and statistically) indicate that Gentian Violet is carcinogenic to mice (B6C3F1). The committee agreed to the recommendation of the Biometrics Staff (HFV-124) that the Virtually Safe Levels (VSL) presented in the NCTR Report be accepted.

BRSonawane

B. R. Sonawane, Ph.D
Executive Secretary of the
CVM Cancer Assessment Committee

cc:HFV-16(2)
✓HFV-100
HFV-102
HFV-140
HFV-150(3)
FT:cgl:12/17/84

February 28, 1985

Acting Director, Policy Development and Quality Control Staff, HFV-102

Gentian Violet (GV)

William B. Bixler, VMD
Director for Surveillance & Compliance, HFV-200

I have read your memorandum of January 10, 1985 to HFV-1 on gentian violet options and Dr. Crawford's decision memorandum dated January 14, 1985. I have also read a draft of the FR Notice asking for voluntary compliance that was prepared by your staff.

I ask that you consider the following comments on these documents.

Your option paper appears to equate informal rule-making (option 2) with treating all firms equally and taking enforcement actions (option 3) with not treating all manufacturers equally. I question this conclusion. Because we published a FR Notice in July 1982 saying we would not take action against the use of 8 ppm GV as a mold inhibitor in poultry feed, it would seem that both options would require publication of a new FR Notice to tell interested parties of our new available information and our new intentions concerning the dye. In addition, both options would almost surely involve taking regulatory action at some time against firms that continue to market the dye. When this time arrives, we could (and should) make an effort to identify everyone making or selling the compound for use in animal feed and take regulatory action against all violators at the same time regardless of which option we follow.

In conclusion, since both options involve putting the regulated industry "on notice" with a FR publication and both will involve regulatory action against those firms that do not stop using the dye in response to our Notice, I fail to see how fairness is a factor in selecting one option over the other.

I agree with your conclusion that the comment and rule-making option would provide a stronger legal foundation for taking regulatory action against GV suppliers. The downside of this option is, as you pointed out in your memorandum, the additional time that consumers would be exposed to residues of the dye in the edible tissues of chickens if this option [illegible]

best copy available

Accordingly, I would like to ask you to estimate for Dr. Crawford's information the time it would take to successfully complete the comment and rule-making procedure.

Mr. Brigham is in the process of finding out if this proposed action must be sent to OMB under Executive Order 12,498 before significant agency resources are expended on it. Even if this does not have to occur, it is my understanding that both the Proposal and the Final Notice will have to cleared through the Commissioner, the Secretary's Office and OMB before they publish. We could well be looking at several years or longer before the Center is in a position to remove residues of this carcinogenic dye from our food supply. How could we defend these delays to consumers when a much faster option i.e., resume taking regulatory action, is available to the Center?

I recognize the potential problems associated with announcing and then reimplementing regulatory action against those who continue to market gentian violet. On the other hand, we brought approximately 25 successful siezure actions and two successful injunctions during the 1960s and 70s when we only thought the dye was carcinogenic. Should we do any less now that we know the compound is carcinogenic and we know that residues above the one-in-one million lifetime risk level for cancer occur in the meat from treated birds?

Finally, the draft FR Notice that I saw last week will not, in my opinion, convince any suppliers or users of GV to voluntarily stop supplying and using the dye. Could we not retain the possiblity of regulatory action as a viable option at least until we have an idea how successful and timely the comment and rule-making approach will be?

Joseph A. Settepani, Ph.D.

cc: GCF-1 (Degnan, Geyer)
HFV-2
HFV-100
HFV-101
HFV-102
HFV-130
HFV-201
PREPARED:JASETTEPANI
R/D:JASettepani:jvp:2/14/85
F/T:jvp:2/28/85
$1.20

Cyclic review & [illegible]

MEMORANDUM DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO Director, Bureau of Foods, HFF-1 DATE: ~~May~~ June 19, 80

Through: Associate Director for Compliance, HFF-300

FROM Director, Food Animal Additives Staff, HFF-350

SUBJECT: Impact of Cyclic Review and SOM regulations

The purpose of this memorandum is to inform you of the possible impact on animal agriculture and the animal drug industry of the planned cyclic review and the SOM regulations.

Background

In June, 1979 the agency was ready to publish in the FEDERAL REGISTER an announcement of the beginning of the cyclic review of new animal drugs. The notice had been "signed-off" by both Bureaus and Deputy Commissioner Gardner. The review of all regulated new animal drugs was to be conducted according to a priority list established by the Bureau of Foods. When the agency completed its review of the available safety information for each drug, the agency would determine under section 512(e) if the drug was shown to be safe, not shown to be safe, or shown to be unsafe. If the drug was shown to be safe, that decision would be announced in the FEDERAL REGISTER. If the drug was not shown to be safe, but no apparent hazard was associated with continued use of the drug for a limited period of time, the sponsor would be allowed to conduct studies and submit the additional safety data required to show that the drug was safe under its prescribed conditions of use. If the drug was shown to be unsafe, the approval of the NADA would be withdrawn through the usual mechanism. The notice was never published. There was internal dissatisfaction with the priority list. In addition, because the agency was imposing a large economic burden on the animal drug industry, it was desirable to provide for public participation through notice and comment rulemaking.

The present plan is to implement the cyclic review through a series of procedural regulations. The revised plan was approved by Acting Commissioner Gardner in a briefing held in October, 1979. An advance notice of proposed rulemaking for the cyclic review and the total residue regulation have been prepared and "signed-off" by the Bureau of Foods.

The proposed review includes all new animal drugs and will be initiated through a regulation requiring a total residue study for all drugs lacking these data. This plan highlights the importance of total residue exposure data to the evaluation of safety. (As a practical matter, nearly all regulated new animal drugs are lacking this study. Either cyclic review plan would eventually require the submission of these data.) A new study will not be required if there is sufficient information available to assess human exposure to the total residue of toxicological concern or if there are expected to be no residues of toxicological concern. The data will be submitted according to a priority scheme based on molecular structure, a use factor, and the date of initial approval for the generic drug substance. Data for drugs that have structural relationships to demonstrated carcinogens will be requested first. All regulated new animal drugs grouped by molecular structure and use factor are listed in Appendix 1. The data for the first 20 drugs will be submitted 1 1/2 years after the effective date of the final order for the total residue regulation. The data for each next group of 30 drugs will be submitted at yearly intervals thereafter. Therefore, if total residue studies are required for all drugs, the data will be submitted over a 5 1/2 year period. From the new total residue data and the agency's review of the previously submitted safety data, the agency will determine for each product under section 512(e) whether the drug is shown to be safe, not shown to be safe, or shown to be unsafe. This determination will dictate the same actions as described above. For those drugs requiring additional testing, the priority and time schedule for testing will be based on unresolved toxicity concerns, human exposure, and the availability of testing facilities. For drugs in the highest priority group, sponsors will be required to initiate testing as soon as the total residue data and the existing toxicity data are evaluated by the agency. Because of the large number variables, including the number of drugs that will require testing, the type of testing required, the availability of test facilities, the number of drugs that will be sponsored, etc., a reliable time frame cannot be predicted. However, it is likely that the first "affirmation of safety" for these drugs will not be possible until 6 years after the effective date of the final order for the total residue regulations.

In determining the safety status of marketed drugs in the review, the SOM safety principles and data requirements will be applied. Thus, the scientific rigor of the SOM regulations will also have an impact on the cyclic review. The agency is in the process of preparing a "final order" on these regulations (last re-proposed on March 20, 1979). These regulations will apply retrospectively to all new animal drugs and will require the rigorous data collection package for those drugs that have the potential to contaminate edible animal products with carcinogenic residues. The present plan calls for implementation of these regulations as a part of the cyclic review. The extent of the data collection package required is determined after applying the threshold assessment guideline of the SOM. A judgement is reached on whether the SOM schedule of data requirements is necessary or whether the general food safety schedule is adequate. The threshold assessment is based on a toxicity factor (consisting of the molecular structure, and the results from genetic toxicity and subchronic or chronic feeding studies), a use factor, and a total residue factor.

Economic Considerations

Regulated new animal drugs that do not have sufficient sales to support the cost of new human food safety studies may be "abandoned" by the sponsor. The average cost of each total residue study is estimated at $100,000, with a range of $60,000-135,000. The large range results from the high cost of testing in cattle with therapeutic doses of radiolabeled drug at high specific activity. These estimates include the cost of the radiolabeled drug, the experimental animals, the laboratory work, the personnel and facilities, and the preparation of the final report. Many drugs will require more than one residue study and most will require analytical method development. Some drugs may require additional toxicity testing. Therefore, a likely cost of testing each generic drug in the cyclic review using general food safety requirements will be $500,000-1 million. The cost of data collection for new drugs subject to the SOM regulation was previously estimated at $4.3 million.

The 1977 sales survey information and the number of residue studies required are summarized in Table I.

Table I

Estimated 1977 Sales	# of Drugs	# of Total Residue Studies*
No Sales Found	30	30
Less than $100,000	22	34
$100,000-500,000	22	36
$500,000-1 Million	14	23
Greater than $1 Million	59	207
TOTAL	147	330

*Because many drugs are approved for use in more than one species and by more than one route of administration, many drugs will require more than one study.

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*Because many drugs are approved for use in more than one species and by more than one route of administration, many drugs will require more than one study.

Assumptions

In order to judge the impact on animal agriculture of the potential loss of these products, several assumptions are made:

1. Assume that drugs with sales greater than $1 million and subject to the SOM will be available if the drug is supported by previously submitted chronic studies that did not indicate carcinogenicity.
2. Assume that loss of products with "no sales found" will have no impact on animal agriculture.
3. Assume that if a therapeutic class has sufficient drugs with sales greater than $1 million, at least some of these will be supported by the animal drug industry and no serious impact on animal agriculture will result.
4. Assume that most of the products listed under Miscellaneous will not require a total residue study because of the accepted "safe" nature of the compound and its residues (e.g. dextran, polypeptides).

Impact of the Total Residue Regulation

Four potential problem areas are identified. It remains possible that problems associated with the loss of specialized use products have not been identified. We have requested that the Bureau of Veterinary Medicine review these lists and alert us to any additional problems.

1. Anesthetics. It is possible that no anesthetics will remain. Methoxyflurane (high sales) may be subject to the SOM. Illegal use of these products in food-producing animals is likely.
2. Antimicrobials. It is possible that no antimicrobials will remain. This class includes the sulfonamides. Furazolidone, Sulfadimethoxine, and Sulfamethazine (each with high sales) will be subject to the SOM. Perhaps antibiotics will be available to treat the specific diseases susceptible to these drugs.
3. Coccidiostats. Several coccidiostats will remain. However, these drugs are assigned a high use factor and most will be subject to the SOM. Many are presently supported by chronic studies and re-testing for carcinogenicity may not be required.

4. **Diuretics.** It is possible that no diuretics will remain. These products are important for treating edema in dairy cows. Furosemide (high sales) may be subject to the SOM.

Impact of SOM Requirements

Implementation of the SOM regulations during the review will have an additional impact. The 21 drugs with sales greater than $1 million that will be or are likely to be subject to these requirements are listed in appendix 2. The continued availability of each of these drugs is discussed below.
The Bureau of Foods has concluded that the existing data demonstrate no increased risk of cancer from the continued use of the Synovex products (Estradiol, Progesterone, and Testosterone). The previously submitted chronic studies did not indicate carcinogenic potential for Amprolium, Carbarsone, Ethopabate, Nicarbazin, Roxarsone, Sulfanitran, or Toalene. These studies may satisfy the requirements of the SOM regulation and extensive re-testing of these products for carcinogenicity may not be required. Because of existing adverse data, it is unlikely that even with additional testing safe conditions of use can be found for Carbadox, Dimetridazole, Furazolidone, and Ipronidazole. The approvals for those products are likely to be withdrawn. Of the remaining drugs (Dibutyltin dilaurate, Ormetoprim, Sulfadimethoxine, Sulfamethazine, Dichlorvos, Furosemide, and Methoxyflurane), only Sulfamethazine has sales in excess of $4 million (the estimated cost of the SOM data package). NCTR will conduct the metabolic and chronic feeding studies on Sulfamethazine. The other products are likely to be "abandoned" by the sponsors.

Some Examples of Possible Alternatives

(These examples are not intended to be all inclusive and need more extensive analysis to determine the advantages and disadvantages of each course of action. In addition further analysis may uncover other viable options.)

1. Proceed with the cyclic review as presently planned and withdraw the approval of products that are "abandoned" by the sponsor.

2. Proceed with the cyclic review as presently planned but slow down the pace of the entire process.

3. Proceed with the cyclic review as presently planned but alter the priority scheme for data collection such that the drugs with low sales and low potential for human exposure to drug residues are not reached for a longer period of time (see Table II).

4. Proceed with the cyclic review as presently planned but propose federal funding of the tests for "critical products" with low sales.

5. Conduct the cyclic review as planned for drugs with high potential for human exposure to residues. Conduct a causal review for drugs with low potential for human exposure to residues. Human food safety data would be required for the latter group only if significant toxicity is demonstrated from available evidence and residues are likely to persist in the food-producing animal.

Robert J. Scheuplein, Ph.D.

cc:
HFF-300 (Quinn)
HFF-350 (Cordle)
HFF-350 (Lipman)
HFF-350 (Benson)
HFF-152 (Flamm)
HFF-154 (Farber)
HFF-458 (Livingston)
HFV-9 (Guest)

RBenson:ljd:0741A:5/30/80

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 21 1985

The Honorable Ted Weiss
Chairman, Subcommittee on Intergovernmental
Relations and Human Resources
Committee on Government Operations
House of Representatives
Washington, D.C. 20515

Dear Mr. Weiss:

This is in further reply to your letter of September 30, 1985, concerning animal drugs.

Enclosed are responses to questions submitted with your letter. If we can be of further assistance, please let us know.

Sincerely yours,

Henry Halleman /for
Hugh C. Cannon
Associate Commissioner
for Legislative Affairs

Enclosures

Question #1

Since 1983, how many unapproved new animal drugs have CVM directed to be removed from the market? During the same period, how many unapproved new animal drugs have been introduced to the marketplace?

Response

During the course of each year, thousands of products receive the attention of CVM with respect to whether they violate the FDC Act or not. The Center annually reviews approximately 2,200 drug experience reports. Such reports contain product labeling which is reviewed to determine continued compliance with the FDC Act and attendant regulations. Additionally, FDA investigators visit animal drug manufacturers periodically to determine their compliance with good manufacturing practices and other requirements. When such inspections are conducted, labels of manufactured products which appear to the investigators to be potentially violative are collected and submitted to CVM for review. CVM reviews approximately 800 labels per year on this basis.

Additionally, the Center, under one of its compliance programs, has had field personnel collect over 2,000 labels over the past several years. These have been submitted to CVM and screened to identify those which represented a significant hazard to human or animal health. As a result of all of these processes more than 112 regulatory actions have been initiated in the past 2 years against firms manufacturing or distributing unapproved new animal drugs. A precise count of the number of products involved is not available but each of the actions cited above may include anywhere from one to a dozen or more products. Thus direct regulatory action has been initiated against hundreds of unapproved new animal drugs in the last 2 years. Most of these actions resulted in the immediate cessation of violative action. However, some are still being contested.

Since FDA does not keep its regulatory activities a secret, many firms beyond those to which the opinion that a particular product is an unapproved new animal drug subject to regulatory action is directly transmitted, may learn of CVM's regulatory position. Some of these may then elect to cease marketing similar products, i.e., they may elect to voluntarily comply with CVM's stated regulatory position.

The products reviewed under the system described above cover the entire spectrum of animal drugs ranging from those which are flagrantly violative and represent a hazard to consumers (either directly or through unsafe residues in food animals) or to the target animals themselves, through those which are approved by the Center, to those which are generally recognized to be safe and effective and adequately labeled.

There are relatively few products in either of these extreme categories. FDA acts rapidly to remove from the market those products which represent a hazard to either humans or animals. Because FDA devotes the bulk of its resources to those situations in which human or animal health are at risk, there are many products currently being marketed which are technically unapproved new animal drugs and which may or may not be effective but to the best of CVM's knowledge are not unsafe. Many topical products like liniments and antiseptics fall in this catergory as well as many oral vitamin/mineral preparations.

While in terms of numbers of products, only a minority of those currently marketed are approved; in terms of numbers of animals treated or exposed to currently marketed products, the overwhelming majority of exposures will be to approved products. Of the exposures to unapproved products, as already noted, the majority of these will be products which CVM believes are relatively innocuous although they may be of questionable effectiveness.

This leaves a group of marketed products, which is not clearly defined, but which number probably well into the hundreds, the representatives of which violate the Act in a manner potentially harmful to animals or consumers. CVM takes regulatory action against such products as they reach its attention and to the extent resources permit. The Center is working to better characterize this group of products and to initiate regulatory action against such products in the most effective manner possible. To this end, and as in the past, CVM will increasingly direct resources toward class actions rather than product-by-product regulatory action. In this context, in the last year CVM has taken class action against vitamin K_3 Parenteral products which were shown to be hazardous to target species and against chloramphenicol products intended for aquarium use because of the potential hazard to human users. Each of these actions will result in the removal of products from the market. In addition, our routine product-by-product (or firm-by-firm) regulatory activities have resulted in the removal of many products from the marketplace as already noted.

At this time it would be difficult to determine how many unapproved new animal drugs have been introduced to the marketplace since 1983. CVM is working hard to update its drug listing system in order to better process information submitted by manufacturers, but in any event information regarding the marketing of unapproved new animal drugs is often not submitted at all. To perform a retrospective analysis of marketing practices over the last 2 years in an effort to determine this number would require an extensive survey and a significant resource expense.

Questions #2

Dr. Crawford testified that, in response to the widespread marketing of unapproved new animal drugs, CVM initiated an extra-label use program designed to ensure a veterinarian/client/patient relationship in the administration of prescription drugs. However, the extra-label use program only covers drugs that have already been approved for at least one use. How does this program address the problem presented by the marketing of thousands of new animal drugs not covered by approved NADAs?

Response

FDA's extra-label use policy is not intended to apply to new animal drugs which are not subject to an approved NADA or are not used to treat nonfood-producing animals. The programs and procedures we use to address marketing of unapproved new animal drugs are discussed in our response to question #1.

Question #3

How many FTEs, broken down by field and headquarters, are currently allocated to the objective of combatting the marketing of unapproved new animal drugs?

Response

For FY '86, 34 field FTEs and 42 headquarters FTEs are allocated to the project area involving monitoring marketed animal drugs and devices. Of this total, 22 field FTEs are planned specifically for surveillance to combat illegal distribution of animal drugs. The precise distribution of both field and headquarters FTEs will, of course, depend on events in the field, especially product emergencies, as the year goes by. However, the Agency has increased the staffyears planned for this activity from earlier levels and intends to maintain the objective of preventing the marketing of unapproved new animal drugs as a high priority.

Question #4

What does FDA estimate to be the cost of bringing CVM into compliance with drug listing and registration requirements?

Response

The Center for Veterinary Medicine (CVM) would require $526,000 (for computer equipment and systems, contracts, etc.) and 4 FTE in order to bring industry into compliance with drug listing registration requirements. The resources would be used to enable CVM to establish a system which will permit the efficient processing of additional incoming drug listing data from increased industry compliance. However, if the drug listing requirements of the Act are to be fully implemented, the Agency would also need to acquire and commit additional field resources to an effort to force manufacturers to comply with the data submission required by the Act.

Question #5

On September 9, 1985, Mr. Clifford Shane advised the subcommittee staff that in both FY '84 and Fy '85 FDA allocated 1.3 person-years to combatting the illegal sale of veterinary prescription drugs throughout the United States. Although his region was allocatd .27 and .30 person-years for this objective in FY '84 and FY '85 respectively, his region is currently using 1 person-year for this purpose. On August 8, 1985, Dr. Beaulieu confirmed that the field has "overburned" the resources allocated to this objective. Have FDA and the Department requested additional resources to meet this problem?

Response

Additional field resources were requested by CVM on March 16, 1984 and FDA reallocated 10 FTEs for the Monitoring of Marketed Animal Drugs and Devices Program area. This covers the Illegal Distribution of Veterinary Prescription Drug Program, as well as special assignments directed at this particular problem, such as:

- Chloramphenicol Investigations Under the Revised CVM Policy on Extra-Label Use of Drugs in Food-Producing Animals, March 1, 1984.
- Banned and Unapproved Animal Drug Survey assignment which issued on July 1, 1985.
- Import inspection assignment which issued in March 1985, which covers imported drugs.

Question #6

Please supply, for fiscal years 1983-86, copies of all CVM submissions requesting additional resources. Also, please indicate whether and, to what extent, CVM awarded any resource increases it had requested.

Response

We have attached CVM's program initial planning requests to FDA for fiscal years 1983 to 1984 which included requests for additional resources. Each fiscal year's requests include a summary of CVM's major objectives as well as a table showing the proposed levels of funding, including increases. We should indicate for the fiscal periods 1983-85 CVM did not receive its proposed increases because the FDA had higher program priorities elsewhere. However, in May 1985 the Center received the FY '86 proposed reallocation of field resources which increased this program's resources by 25 FTEs.

Explanation of Abbreviations Used in Resource Distribution Tables

FY 86, 85, 84 Resource Tables

Maint = Maintenance Level (no increase or decrease)

FY 83 Resource Table

Mi = Mininum Level (lower than Maintenance Level)

Ma = Maintenance Level (no change)

L = Low Level (a low or moderate increase)

D = Desired Level (no constraints as to level of increase)

ANIMAL DRUGS AND FEEDS

SUMMARY OF FY 86 PLANS

During FY 86, the Animal Drugs and Feeds program will operate within a six-project PMS instead of the five as in the past. The added PMS project, Voluntary Compliance, is designed to further centralize responsibility for complying with the Food, Drug, and Cosmetic Act (FD&C Act) by the regulated industry. The remaining five PMS projects are essentially the same. All position distribution data and dollar distribution data herein have been adjusted as accurately as possible to reflect the new structure.

During FY 86, the Animal Drugs and Feeds program will focus on specific objectives to strengthen and broaden the scientific base. Program professionals will be involved to a greater extent in research to help foster an attitude of cooperative scientific development with the veterinary medicine and public health communities, academia, and industry. The expansion of the science base will enable the program to exercise a more significant role with respect to public health considerations and serve to provide a focus on minor use animal drug development.

The program held its first strategic planning workshop at Harper's Ferry in June 1983. The following policy issues were identified and prioritized:

1. Monitoring the manufacture, distribution, labeling, and use of veterinary drugs and devices, thereby reducing illegal veterinary drug distribution and use.

2. Enhancing the scientific capacity of the program to identify new technologies and resolve state-of-the-art issues in veterinary medicine.

3. Establishing procedures for evaluating adverse drug experience from marketed drugs and devices.

4. Increasing compliance with the FD&C Act by the regulated industry through the use of voluntary compliance activities.

5. Improving the program's scientific base for rendering sound regulatory decisions on animal feed contaminants.

The prioritization of the program's PMS obligations is intended to reflect its needs and to help achieve these crosscutting objectives.

ANIMAL DRUGS AND FEEDS

FULL-TIME EQUIVALENTS (FTEs) AND DOLLAR DISTRIBUTION ($000)*

Resource Category	FY 84	FY 85	FY 86 Maint.	Change from FY 86 Maint.	
				FY 86 Reduction	FY 86 Increase
Headquarters FTEs	255	252	252**	-15.5	18
Field FTEs	164	163	163	-10.5	8.
TOTAL FTEs	419	415	415	-26.0	26
FTE Dollars	/////	/////	/////	-1,040	1,040
Project Contract Dollars	906	840	840	-460	60
State Contract Dollars	966	966	966	0	0
Grant Dollars	43	200	200	0	0
Other Dollars	-	-	-	0	0
TOTAL DOLLARS	/////	/////	/////	-1,500	1,100

* This distribution indicates how the bureau/center would allocate the FY 86 levels.
** Includes reallocation

ANIMAL DRUGS AND FEEDS

SUMMARY OF FY 85 PLANS

The recent transfer of the human food safety aspect of animal drug reviews from the Bureau of Foods to the Bureau of Veterinary Medicine added significantly to BVM's program responsibilities. New initiatives for FY 85 represent both intramural and extramural research activities including the pathophysiological research on environmental and natural toxicants in animal feeds. The program will continue to develop voluntary quality assurance programs to prevent potential contamination incidents. In addition, if granted an increase over the FY 85 "maintenance" level, the Safety of Animal-Derived Human Foods project will provide BVM "consumer" and "provider" constituencies information and education services.

The Monitoring of Marketed Animal Drugs and Devices project will place emphasis on the importance of prioritizing surveillance and compliance activities to maximize effective use of available resources. In addition, it will reevaluate and modify the compliance programs, which generate those regulatory actions, so that the Agency can best utilize its resources. With increased resources the Bureau could plan additional inspections and investigations of animal drug importers and consignees in FY 85.

In the New Animal Drug Evaluation area, efficiency of processing the applications will be improved so that 85% of 3,000 receipts will be reviewed within the statutory timeframe. The emphasis will be on continued use of the Expedited Review in processing and monitoring of applications. In addition, applications for minor use/orphan animal drugs will be reviewed in the most efficient manner.

In the Animal Feed Safety area, emphasis will be on continued implementation of new medicated feed projects, especially in inspectional coverage by FDA and the states including medicated premix manufacture.

FY 1985

ANIMAL DRUGS AND FEEDS

FULL-TIME EQUIVALENTS (FTEs) AND DOLLAR DISTRIBUTION ($000)*					
Resource Category	FY 83	FY 84	FY 85 Maint.	Change from FY 85 Maint.	
				FY 85 Reduction	FY 85 Increase
Headquarters FTEs	251	249	249	- 10	14
Field FTEs	161	160	160	- 10	1
TOTAL FTEs	412	409	409	- 20	15
FTE Dollars	/////	/////	//////	- 700	525
Project Contract Dollars	1,114	841	841	- 405	1,170
State Contract	741	741	741	0	0
Grant Dollars	55	50	50	0	0
Other Dollars	/////	/////	/////	0	280
NADIS	760	760	760	0	0
TOTAL DOLLARS	/////	//////	/////	-1,105	1,975**

* This distribution indicates how the bureau/center would allocate the FY 85 levels.

** Exceeds planning "increase" mark of $1,100.

FY 1984

ANIMAL DRUGS AND FEEDS

FULL-TIME EQUIVALENTS (FTEs) AND DOLLAR DISTRIBUTION($000)*					
Resource Category	FY 82	FY 83	FY 84 Maint.	Change from FY 84 Maint.	
				FY 84 Reduction	FY 84 Increase
Headquarters FTEs	223	221	221	-27.5	22
Field FTEs	164	162	162	-14.5	3
Bureau of Foods	53	53	53	-4	0
TOTAL FTEs	440	436	436	-46	25
FTE Dollars	////	////	////	-1,610	875
Project Contract Dollars	802	[redacted] 836	[redacted] 836	-315	320
State Contract	643	643	643	0	95
Grant Dollars	50	55	55	0	0
Facility Dollars	////	////	////	0	0
Other Dollars	////	////	////	-75	110
BF Contract Support	1,200	1,200	1,200	0	0
TOTAL DOLLARS	////	////	////	-2,000	1,400

* This distribution indicates how the bureau would allocate the FY 84 levels.

BUREAU OF VETERINARY MEDICINE

SUMMARY OF FY 83 PLANS

CENTRAL THEME

During FY 83, the Animal Drugs and Feed Program will continue to focus on the surveillance of animal feed ingredients and animal drugs in interstate commerce and the fastest possible response to all types of applications for approval of animal drugs and medicated feeds to reduce the numbers which are permitted to exceed statutory time frames for review. Scientific activities will continue to be supported by intramural and extramural research programs in selected areas. The program will continue to develop voluntary quality assurance programs to prevent potential contamination incidents, and our Emergency Response Program, including its team of experts, will continue to be ready to provide quick response to assist in speedy resolution of animal contamination incidents, affecting public health. Attention will continue to be given to the Regulatory Flexibility Act, implemented on January 1, 1981, which made it mandatory to actively consider the impact and involvement on small business entities during the regulation development process.

In the Animal Feed Safety area, greater attention will be given to field surveillance/compliance activities and to headquarters-directed contract research. Emphasis will be placed in the following activities: continued implementation of the new medicated feed program especially in inspectional coverage by FDA and the states; surveillance of animal feeds and feed ingredients for the presence of mycotoxins, pesticides, industrial chemicals and heavy metals; research designed to assess the effects of low-level exposure to mycotoxins on the immune response of food-producing animals and research designed to evaluate human and animal effects resulting from the continuous feeding of low levels of antibiotics to food-producing animals.

In the New Animal Drug Evaluation area, efficiency of application processing will be improved so that 87 percent of 3700 receipts will be reviewed within the statutory time limit. Our "Fast Track" priority review program, new since the summer of 1980, will continue to speed processing of the most important new animal drug applications. Approximately 20 new molecular entities will require intensive priority review with current available resources and reallocation of review resources. The new emerging DNA technology requires training of present staff and hiring of specialized scientific personnel. The emphasis will be on monitoring statutory time frames for all applications with reallocation of resources to newer concepts such as "Fast Track" and DNA applications. The objective of the program will be the cost efficient review of applications for new animal drugs.

In the Safety of Animal-Derived Human Foods area, in order to maintain a low backlog and short turn-around time for handling pending applications and petitions, and to allocate resources to preparation of food safety guidelines, the planned re-evaluation (cyclic review) of human food safety aspects of marketed animal drugs will be somewhat curtailed. Given additional resources, this project plans to staff a tissue residue surveillance function which would assimilate reports on residue monitoring conducted by FSQS/USDA and those from FDA's field investigators, with input being made into the program's compliance activities on tissue residues. Given further additional resources, some extramural research in the area of developing analytical methods for confirming antibiotic residues in animal-derived human foods will receive high priority.

In the area of Monitoring Marketed Animal Drugs and Devices, emphasis will be placed on the importance of prioritizing surveillance and compliance activities to maximize effective use of associated resources. The program will increase its responsiveness in processing regulatory actions affecting animal drugs and devices. It will reevaluate and modify the compliance programs which generate those regulatory actions so that Agency resources are used to the best advantage. Emphasis will be placed on achieving such objectives as follows: increasing the timeliness of processing proposed regulatory actions; increasing the efficiency and effectiveness of recall and health hazard evaluation procedures; maintaining the veterinary drug adverse reaction program; causal review of NADA's and more timely processing of congressional, state, and consumer inquiries.

In the Animal Drugs: Bioresearch Monitoring area, the program will conduct inspections to ensure that the quality and integrity of bioresearch data for animal and feed additives are sufficient and reliable to warrant approval of New Animal Drug and Medicated Feed Applications. In addition, our Bioresearch Monitoring Project will conduct regulatory actions to ensure Good Laboratory Practice and Clinical Investigation compliance.

DOLLAR DISTRIBUTION

($000)

The distribution below indicates how the bureau would allocate the FY 83 levels.

	FY 80	FY 81	FY 82	Change From Previous Year FY 83 Mi	FY 83 Ma	*** FY 83 L	Change From FY 83 Low FY 83 D
Position Dollars	////////////	////////////	15,192	-1,085	0	665	4060
Project Contract Dollars	1,099	2,560 **	1,525	- 215	0	204	3220
State Contract Dollars	986	750	834	0	0	131	131
Grant Dollars	35	85	55	0	0	0	0
Facility Dollars	////////////	////////////	////////////	0	0	0	0
Other Dollars*	////////////	////////////	////////////	0	0	0	0
BF Contract Suppt	335	1,207	1,200	0	0	0	675
	////////////	////////////	////////////				
TOTALS				-1,300	0	1,000	8086

* Activities that were not specific to a single PHS project (i.e., extraordinary operating costs and bureau-wide activity costs).

** Includes $1.5 million one-time Congressionally mandated research on Antibiotics in Animal Feeds.

*** Represents increase level

POSITION DISTRIBUTION

The distribution below indicates how the program would allocate the FY 83 levels.

				Change From Previous Year			Change From FY 83 Low
	FY 80	FY 81	FY 82	FY 83 MI	FY 83 Ma	* FY 83L	FY 83 D
Headquarter Positions	229	229	229	-20	0	10	67
Field Positions	137	166	166	-7	0	8	41
BF Support	41	41	41	-4	0	+1	8
Total	407	436	436	-31	0	19	116

* Represents increase level

Question #7

In a January 14, 1980, memorandum on agency recommendations for a cyclic review of animal drugs, Dr. Robert J. Scheuplein, then Director, Food Animal Additives Staff, wrote that "[m]ost marketed animal drugs have been approved on the basis of safety evaluations currently considered inadequate" and that "it is very likely that if all . . . approved drugs were re-evaluated in the light of current science and policy, that several couldn't meet the 'shown to be safe' standard and that many more would require revised tolerances." In a July 9, 1980, memorandum to the Commissioner, Dr. Crawford wrote that he thought it was neither economically nor politically feasible to ask industry to produce additional data to support the safety of their already approved drugs. Cyclic review of animal drugs, therefore, was never undertaken. Is it FDA's position that re-evaluations of whether animal drugs still meet the safety requirements of law should be based on economic or political rather than safety grounds?

Response

No. Although Dr. Scheuplein's memorandum dealt specifically with human food safety, nonetheless, as a general proposition, it is simply not scientifically necessary for all approved new animal drugs to undergo a "cyclic review." Rather, CVM utilizes a causal review system. When specific safety concerns arise about approved animal drugs FDA has re-evaluated the data supporting approval of the NADAs and, if appropriate, withdraws approval for these drugs. Some examples are DES, nitrofurans, and the oral solution usage form of chloramphenical.

Question #8

Cyclic review of animal drugs was intended to include a re-evaluation of whether existing regulatory methods for detecting animal drug residues met current guidelines, since most of the animal drugs for which adequate methods are unavailable were approved many years ago. Inasmuch as development of practicable methods for detecting animal drug residues is a condition of NADA approval, Dr. Crawford testified that FDA "will have to take action to take . . . off the market" any drug for which adequate detection methods cannot be developed. What timetable has FDA established to ensure that approved new animal drugs in use are supported by adequate methods for detecting their residues and those of their metabolites in milk and edible animal tissues? Has FDA advised sponsors of the deadlines they must meet for developing such methods?

Response

Cyclic review was intended to include a re-evaluation of existing methods; however, the absence of a method by itself has not been sufficient to justify a timetable or an official notification to the sponsor of a pending regulatory action. Notification has been used only when there has been sufficient concern to justify an action all the way through to a possible hearing. To base actions solely on the absence of methods would not be the best use of Agency resources. Drugs which present specific safety concerns, such as carcinogenicity, have taken precedence. Nitrofurans have been the highest priority drugs and are presently in a hearing. Other drugs such as dimetridazole and ipronidazole will be evaluated once their carcinogenicity is resolved and safe concentrations established.

The Agency has also embarked upon an initiative to evaluate methodology needs, prioritize those needs, and work with USDA and the sponsors toward development of necessary methods. This will be a long term project and at this point, no timetable has been established.

Question #9

Has FDA ever defined for sponsors what constitutes the required specificity for a regulatory method?

Repsonse

FDA has discussed the requirements for specificity in numerous speeches and the published sensitivity of method document of March 20, 1979. No quantitative definition has been given to sponsors as none exists. For practical purposes, gas chromatography/mass spectrometry is the only procedure that we accept that the requirements have been delineated in detail. Dr. Sphon of the Center for Food Safety and Applied Nutrition has published two papers, in addition to several formal presentations, on our requirements for mass spectrometry for confirmation of animal drug residues. Other methods of confirmation are extremely subjective; hence, no requirements have been given to sponsors.

Question #10

Have there been any additional updates of the 1972 Johnson memorandum since 1979? If so, please provide copies of all such updates.

Response

No. The "Andres" Report of 1979 was the last comprehensive review of methodology undertaken by the Center (see attachments).

READEX FICHE

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : The Commissioner
Food and Drug Administration

DATE: DEC 28 1979

FROM : Committee to Analyze Presently
Approved Detection Methods of Food Animal Feed Additives

SUBJECT: Evaluation of Approved Drug Residue Detection Methods for Food Animal Feed Additives - ACTION

As per then Acting Commissioner Sherwin Gardner's memorandum of July 19, 1979, we present for your consideration our evaluation of analytical methods for approved feed additive drugs used in the monitoring of residues in food producing animals. Our evaluation was based on an analysis of analytical methods using the current criteria and approval process for regulatory assays.

Resultant from these deliberations the committee submits it's recommendations concerning actions to upgrade this area. The committee feels that if there are any areas that need clarification this can be accomplished either verbally or in writing at your discretion.

Carolyn N. Andres

Carolyn N. Andres, Chairman
Supervisory Chemist - HFR-8160
Veterinary Analytical Section
Denver Field Office
Executive Directorate for Regional Operations

Edward H. Allen

Edward H. Allen, PhD.
Chief, Chemistry Branch - HFV-500
Division of Veterinary Medical Research
Bureau of Veterinary Medicine

Patricia N. Cushing

Patricia N. Cushing
Senior Scientific Reviewer & Microbiologist
Document Review Branch - HFV-234
Division of Compliance
Bureau of Veterinary Medicine

Thomas Fazio
Chief, Analytical Additives Branch - HFF-459
Division of Chemistry and Physics
Bureau of Foods

Thomas Fazio by CM

Edmund I. Kovach
Chemist, Therapeutic Drug Branch - HFV-138
Division of Drugs for Swine and Minor Species
Scientific Evaluation
Bureau of Veterinary Medicine

Robert C. Livingston, PhD.
Chief, Food Additives and Animal Drugs - HFF-458
Chemistry Evaluation Branch
Division of Chemistry and Physics
Bureau of Foods

Robert C. Livingston

John R. Markus
Chief Chemist - HFV-104
Scientific Evaluation
Bureau of Veterinary Medicine

John R. Markus by CM

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Ms. Carolyn Andres, Denver District Office
Dr. John Howard, Bureau of Foods
Dr. Thomas Fazio, Bureau of Foods
Mr. Edmund Kovach, Bureau of Veterinary Medicine
Dr. Edward Allen, Bureau of Veterinary Medicine

DATE: JUL 19 1979

FROM : The Acting Commissioner

SUBJECT: Committee to Analyze Presently Approved Detection Methodologies of Food Animal Feed Additives

I would like you to serve on a committee to analyze the presently approved detection methodologies of food animal feed additives. As you perhaps know, the validity of some of these methods has been questioned. I would charge you as a committee to consider the various tests and render a judgment as to whether each test is valid, not valid, or needs more work before a determination can be made.

This is a very important first step in our current initiative to thoroughly assess animal drugs for food producing animals. I would appreciate Ms. Andres serving as chairperson. I anticipate a report by the first of the year (1980). I wish to thank each of you in advance for the fine job I know you will do in this all important area.

Sherwin Gardner
Sherwin Gardner

cc: Dr. Miller/HFF-1
Dr. Crawford/HFV-1
Mr. Healton/HFO-1

EVALUATION OF APPROVED DRUG RESIDUE DETECTION METHODS FOR FOOD ANIMAL FEED ADDITIVES

SUMMARY

This Committee was charged by Acting Commissioner Gardner on July 19, 1979, to ascertain the validity of tissue residue methods for new animal drugs approved for use in animal feeds. The task force was composed of members from BF, BVM, and EDRO. Members of the Committee were as follows:

Carolyn Andres, Chairman, (Chemist), HFR-8160/DEN-FO
Edward Allen, Ph.D., (Chemist), HFV-500
Patricia Cushing, (Microbiologist), HFV-234
Thomas Fazio, (Chemist), HFF-459
Edmund Kovach, (Chemist), HFV-138
Robert Livingston, Ph.D., (Chemist), HFF-458
John Markus, (Chemist), HFV-104

Over sixty drugs listed in 21 CFR 558 were reviewed. The review was based on the current criteria for regulatory assays. These criteria are discussed in the FSQS (USDA)/FDA Work Group report of June 19, 1979 "Assessment of Criteria Used in Evaluation of Microbiological Tests for Antibiotic Products" (Attachment I) and the SOM proposal (Federal Register 44, #55, 17070-17114, 1979). As was noted in the Work Group report, the criteria for noncarcinogenic drugs are the same as for carcinogenic drugs except for omission of the L_m concept.

There is no drug that meets today's standards for regulatory methodology in totality. Only six drugs (Section IA below) either have both acceptable determinative and confirmatory methods or do not necessarily require a confirmatory test. These, however, lack adequate metabolic and total residue data, as do all the other drugs reviewed. Metabolic and total residue data may precipitate the need for new methods if they indicate that current methods do not measure the depletion of all drug-related residues of toxicological concern.

Five antibiotic drug methods (Section IB) have been considered provisionally acceptable as these microbiological quantitative methods also provide some degree of specificity. However, these methods are not as specific as chemical tests. These microbiological methods, as all other methods, were accepted based on the requirements at the time of approval. The referenced FSQS (USDA)/FDA Work Group Report recommended reassessment of all antibiotic methods.

Six other drugs (Section II) have acceptable determinative methods but lack a confirmatory procedure.

A total of 36 drugs (Section III) have inadequate determinative and no confirmatory methods. Most of these drugs were accepted with limited or no validation data. In essence, the methods are antiquated by today's standards. They lack specificity, accuracy and sensitivity. Total residue and metabolic data are essential before it can be determined what the proper marker residue(s) (parent/metabolite) should be. The antibiotic methods, in particular, are suspect since they measure only the microbiologically active portion of the compound. Inactive metabolites or degradation products are not detected. A shift from microbiological to chemical methods may be mandated for products which have persistent and/or microbiologically inactive residues of toxicological concern.

The remaining drugs (Section IV) either have been withdrawn from the market, are not presently marketed or are for non-food producing animals.

Inclusive in the above summaries are 10 drugs which have zero withdrawal time or are fed with another drug which has a longer withdrawal time. The requirement for surveillance methods for these drugs are of low priority.

A categorization of the drug tissue residue methods is as follows:

I. Drugs with acceptable determinative and confirmatory methods:

A. Chemical Methods

Arsanilate sodium [1]

Arsanilic acid[1]

Carbadox

Carbarsone[1]

Melengestrol acetate

Roxarsone[1]

B. Microbiological Methods. (These microbiological methods may not be as accurate/specific as chemical tests and may be subject to further review):

Bambermycins
Lasalocid sodium
Lincomycin
Monensin
Penicillin, Procaine penicillin

II. Drugs with acceptable determinative but no confirmatory method:

- Clopidol
- Ipronidazole
- Nicarbazin
- Pyrantel tartrate
- Robenidine HCl
- Zoalene[2]

III. Drugs with inadequate determinative and no confirmatory method:

- Aklomide
- Amprolium[3]
- Bacitracin[2]
- Chlortetracycline
- Coumaphos[2]
- Decoquinate[3]
- Dichlorvos[2]
- Dimetridazole
- Erythromycin thiocyanate
- Ethopabate[3]
- Famphur
- Furazolidone
- Hygromycin B
- Levamisole HCl
- Neomycin
- Nitrofurazone
- Nitromide
- Novobiocin
- Nystatin
- Oleandomycin[2]

Ormetoprim[3]
Oxytetracycline
Poloxalene
Reserpine
Ronnel
Streptomycin
Sulfonamides (general - includes sulfadimethoxine, sulfaethoxypyridazine, sulfamerazine, sulfamethazine, sulfathiazole, sulfanitran).
Tetracycline
Thiabendazole
Tylosin
Virginiamycin[2]

IV. Drugs withdrawn from the market, not presently marketed, or used in non-food producing animals:

2-Acetylamino-5-nitrothiazole[4]
Ammonium chloride, feed grade
Buquinolate
Chlormadinone acetate
Diethylstilbestrol[4]
Ferrous fumarate
Griseofulvin
Nequinate
Niclosamide
Styrylpyridinium chloride, diethylcarbamazine (as base)

[1] Arsenic residue - no confirmatory method required. Toxicological effect of the organic degradation product is unknown. Metabolic studies have not been done.

[2] Requirement for a regulatory confirmatory method is of low priority. Drug has zero withdrawal time based on depletion studies. Antimicrobial methods were used to determine depletion times for the antibiotics. Toxicity of microbiologically inactive metabolites is not known.

[3] Drug is most commonly used in combination with drugs having longer withdrawal times - regulatory method is of low priority.

[4] Withdrawn from the market.

INTRODUCTION

Approximately 60 drugs or drug combinations are listed as approved for use in animal feeds under the provisions of 21 CFR 558. The requirements for approval have varied considerably. Initially, little concern was given to drug residues appearing in the edible tissues of food producing animals. Increasing toxicological concern for the residues of drugs have been paralleled by the development of more stringent analytical requirements for the analysis of drug residues. Only a few of the approved feed additive drug tissue residue methods meet current analytical standards.

LEGISLATIVE BACKGROUND

Prior to 1958, a premarket review of animal drugs for human safety was not required by the Federal Food, Drug, and Cosmetic Act. In 1958, approval of drugs for animals was required under 21 CFR 505. However, the safety provision of this part of the Act relates only to the safety of the drug to the target animal and not to human safety. Of the 60 drugs or drug combinations currently approved for use in animal feeds (21 CFR 558), approximately 25% were approved prior to 1958.

In 1962, the "DES proviso" was enacted. This provision allows the use of a cancer causing food additive, new animal drug, or color additive in a food-producing animal when the product will not adversely affect the animal for which it is intended and when no residue will be found in the edible tissues of an animal by an approved method. This proviso provided the first consideration for human food safety from residues in food resulting from the use of drugs in food producing animals.

The New Animal Drug Amendments of 1968 consolidated the scattered provisions relating to animal drugs. These amendments incorporated for the first time language directing the Agency to consider, among other factors, "the probable consumption of such drugs and of any substance formed in or on food because of the use of such drugs" in its premarket safety evaluation. For the first time, all marketed animal drugs subjected to a regulatory tolerance required a tissue residue method. Approximately 75% of the currently approved feed additive drugs were approved prior to the 1968 Amendment.

From 1968 to 1974, most drugs were regulated on the basis of the depletion characteristics and toxicity testing of the parent drug. In 1974, the Agency began routinely requiring total residue studies as part of its premarket safety evaluation. Less than 3% of the currently approved food additive drugs have been regulated on the basis of total residues.

METHOD REQUIREMENTS BACKGROUND

Prior to 1958, regulatory analytical methods were not required. Between 1958 and 1965, method requirements were based only on the potential for possible gross misuse of the drug or on the likelihood of residues occurring. During 1965-1971, residue methods were required and tested on a selective basis at an FDA Headquarters Laboratory; however, the criteria used in judging their acceptability were far below present day standards.

During the transition period of 1971-1972, changes were made in the criteria for acceptance of a regulatory method for drugs used in food producing animals. Laboratory trials of a proposed regulatory method then became a routine requirement. In 1972, laboratory methods trials were extended to include participation of the USDA. Concurrently, the use of dosed tissue was instituted as a requirement in methods trials. Since 1973, a confirmatory assay has been required for approval of new animal drugs. During 1974, total residue studies, which consider metabolites as well as parent drug residues in tissues, were routinely requested prior to approval of new animal drugs. In 1975, total residue requirements were extended to new antibiotic fermentation products (mycelial biomass).

CYCLIC REVIEW OF MARKETED DRUGS

In 1980, the FDA will institute a cyclic review of marketed drugs approved for use in food producing animals. This review will ascertain whether a marketed drug meets the current standards for drug approval. The re-evaluation will be conducted according to a priority list currently being established with those drugs of most concern being initially reviewed, e.g., carcinogens.

The re-evaluation will include a determination whether or not existing regulatory assays meet current guidelines. It is anticipated that either most assays will not meet current standards or that, as a result of total residue requirements and new toxicity information, existing assays will have to be revised. Thus for the majority of currently marketed animal drugs, new assays may have to be devised or old assays up-dated according to current standards.

EVALUATION CRITERIA FOR TISSUE RESIDUE METHODS

The task force evaluated the tissue residue methods approved or sanctioned for use in feeds for food producing animals under 21 CFR 558. The review was based on the current criteria for regulatory assays (Attachment I) and the SOM proposal except for omission of the L_m concept. Review findings for each drug, including comments, are tabulated in Appendix I and discussed in the summary.

MANPOWER COMMITMENTS/METHODS VALIDATION PROCEDURE

Validation is the only mechanism to assure FDA that the proposed method does in fact work. Because of demands which are perceived at the highest administrative levels as more pressing by both FDA and USDA, there has never yet been sufficient commitment of resources to allow adequate attention to validation procedures. Moreover, fractionation of responsibilities among three FDA Bureaus (Foods, Drugs, and Veterinary Medicine) and the Department of Agriculture has contributed to the dilution of authority to set goals and see that they are met.

Currently, the manpower commitments to the method validation program are provided by the Bureau of Foods (Division of Chemistry and Physics), Bureau of Drugs (NCAA), EDRO, and USDA. USDA participates because they must monitor for possible residues once a drug is approved. Their input is most important because of their day to day monitoring of the food supply. Their participation is provided for under a Memorandum of Understanding (MOU). Cooperative interaction of all these groups is vital to a successful validation program.

The main problem that exists in the method trial procedure is the timely commitment of all parties. In some cases, the trials are not given priority in the laboratories. Many studies have lingered on for months. This causes embarrassment for FDA and delays decisions.

A BVM compliance program (CP- 71004) provides time (2 MY) for method validation trials to be conducted at the Denver District Laboratory. Other field laboratories may be used to participate should the need arise. BF also provides time (1MY) for method validation trials. These are the only prorated time commitments for tissue residue methods. USDA and NCAA, on the other hand, must use available time from their normal laboratory work.

If FDA and USDA are committed to improving the validation of methods-screening, determinative, or confirmatory- they must dedicate full time positions (residue analysts-chemists and/or microbiologists) to this activity. These analysts must be left alone to do their work. Adequate resources and support should be provided for performance of these tests as a primary function with minimum interference from other assignments. These problems have been addressed by previous tasks forces (see Attachment I, Part B).

An office, the Acting Associate Director for Human Food Safety, was recently established in BVM to aid in the coordination of NADA related problems with the BF. The office is headed by Dr. Gerald Guest with a small staff. This staff/office is expected to be an asset in bringing about resolution of the problems that beset the method trial procedures.

CURRENT ANALYTICAL REQUIREMENTS

During the last several years there has been a trend toward the implementation of more stringent requirements for data to support the tissue residue methods. It is expected that lower residue levels and even more stringent data requirements will be established for carcinogenic residues in the near future. These requirements, for the most part, concerned with the determination of carcinogenic drug residues in animal tissues at part per billion (ppb) or part per trillion (ppt) levels, are such that an effective and reliable regulatory program will be extremely difficult to execute. Although there have been notable advances in instrumental techniques to detect chemicals, there remains the very difficult problem of applying these analytical techniques to samples of biological material so as to reliably detect, measure, and confirm the presence of residues at these levels. The methods developed for these low levels are time consuming and difficult, since they involve the isolation of minute quantities of the chemicals from complex tissue matrices.

From the point of view of the USDA/FSQS staff which performs the actual meat and poultry residue monitoring function, current requirements are unwieldy, unrealistic, and detrimental to practicable consumer protection. For example, since the USDA can act on presumptive evidence where FDA cannot, USDA found the nonspecific antibiotic depletion methods in NADA's suitable for their detection monitoring purposes. These relatively simple microbiological plate assay methods permit USDA to screen large volumes of tissue samples in a timely manner. Specific methods at required sensitivity levels such as those necessary for FDA legal action are incompatible with the day to day demands of a residue monitoring program. They require specialized instrumentation, highly trained/skilled analysts, and excessive time. All those factors significantly reduce the coverage less sophisticated methods can provide.

The ever changing and growing sophistication of toxicology and chemistry has exerted tremendous influence on the approach to residues evaluation. The concept of total residues (i.e. parent compounds and metabolites) to be monitored via a marker compound in a target tissue has radically changed the determinative feature of residue monitoring, regardless of what may have been deemed adequate in the past. So even the few validations which have been completed may be negated in retrospect by the cyclic review process.

RECOMMENDATIONS

The committee, in its evaluation of the analytical methods, recommends the following actions be undertaken to provide better consumer protection:

1. The following drugs should be accepted under the circumstances proposed below:

   a. The six drugs in Section I of the Summary (arsanilate sodium, arsanilic acid, carbadox, carbarsone, melengestrol acetate, roxarsone) that have acceptable determinative and confirmatory methods or do not necessarily require a confirmatory test should be accepted for use in the BVM compliance program.

   b. The five antibiotic drugs in Section IB (bambermycins, lasalocid sodium, lincomycin, monensin, penicillin, procaine penicillin) that have provisionally acceptable methods should be given sanction for compliance purposes. It is also recommended that further research be performed on a first priority basis to develop better confirmatory procedures.

   c. The six drugs in Section II (clopidol, ipronidazole, nicarbazin, pyrantel tartrate, robenidine HCl, zoalene) that have acceptable determinative methods, but lack confirmatory procedures, should be given sanction for compliance purposes. It is recommended that research on a second priority basis be performed to develop confirmatory procedures.

   d. Residue methods should be developed for the drugs remaining in Section III, taken in order of priority. Simple adjustments in methods which were found unacceptable will not make these methods acceptable. The deficiencies in these methods are major as they are not specific, sensitive, or reliable with respect to the current methods criteria now used by the Agency. In the selection of drugs for methods development, attention should be paid to knowledge of husbandry practices with emphasis on those drugs which can serve as indicators for those with which they are commonly combined. It is the concensus of the committee that new methods development must have a fresh start by careful evaluation of the analytical techniques available today. Until new methods are developed under present criteria, we recommend that compliance actions should be undertaken for these drugs based on (1) investigational evidence and (2) unofficial validation of a method (controls, recovery, precision, accuracy, etc). A BVM/BF/EDRO Task Group should be set up to establish usable guides.

2. Emphasis should be placed on development of multi-residue screening procedures (in particular, sulfonamides and chemical methods for classes of antibiotics) with confirmatory reinforcement where necessary. The development of a monitoring procedure for each chemical residue is impractical since it is not possible to apply hundreds of different methods simultaneously. Therefore, the chemical residues must be placed in groups for which one screening method can be developed to detect the entire group simultaneously. The Food & Drug Administration itself should assume this responsibility via allocation of in-house resources including sponsorship of research contracts where feasible. Additional funds and personnel positions are needed for both intramural and extramural development of this research area. There is no legal authority for FDA to require industry to provide this data and it is unrealistic to assume that industry will accept this burden.

3. FDA should initiate a drug residue monitoring program for milk and eggs. These foods are in the highest food volume category and span the total human life cycle.

4. Commitment to the validation process should be given higher priority by both USDA and FDA. In behalf of the Agency, Dr. Gerald Guest, the Acting Associate Director for Human Food Safety, should obtain a joint validation commitment between USDA and FDA.

5. BF scientists should be consulted more often in the evaluation of analytical evidence on tissue residues before legal actions are initiated and in providing expert testimony. This interaction would insure that the pre-market approval requirements for analytical methods are appropriate to support regulatory actions.

6. The Agency should be made aware of the limits of technology and human resources requirements for tissue residues monitoring. It is essential that the Agency recognizes there is no ideal procedure or method that is simple, specific, and sensitive. It should also be stressed that the consumer may be best served by a sum total of evidence approach rather than by dogged insistence on absolutes. Failure to prosecute flagrant violators based on less than perfect assay methods is abdication of responsibility to the consuming public.

7. Establish administrative/scientific focal points in USDA and FDA to coordinate drug residue monitoring programs.

Appendix i

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Drug	2-Acetylamino-5-nitrothiazole
Drug classification	
CFR Title 21 Regulation	558.25
Earliest approval date	
Animal species	
Tolerance levels/tissues	
Current residue methodology	
Type of determinative step	-
Sensitivity	
Validation	
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	
Metabolic studies	
Total residue studies	
Conclusions	

Drug has been withdrawn from the market - 7/79.

Drug	**Aklomide**
Drug classification	**Antiprotozoal**
CFR Title 21 Regulation	**558.35**
Earliest approval date	**09/09/66**
Animal species	**Chickens**
Tolerance levels/tissues	**4.5 ppm liver/muscle** **3.0 ppm skin/fat**
Withdrawal period	**None**
Current residue methodology	
Type of determinative step	**Spectrophotometric**
Sensitivity	**0.1 ppm**
Validation	**None**
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	**None**
Metabolic studies	**None**
Total residue studies	**Inadequate**

Conclusions

Determinative method is essentially ion exchange and Bratton-Marshall color development. Parent drug and metabolite can be determined.

Confirmatory method needed to differentiate from other sulfonamides.

Drug	Ammonium chloride, feed grade
Drug classification	
CFR Title 21 Regulation	558.45
Earliest approval date	
Animal species	
Tolerance levels/tissues	
Current residue methodology	
Type of determinative step	
Sensitivity	
Validation	
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	
Metabolic studies	
Total residue studies	
Conclusions	

Drug is not marketed.

Drug	**Amprolium**
Drug classification	**Antiprotozoal** **Coccidiostat**
CFR Title 21 Regulation	**558.55, 58**
Earliest approval date	**01/11/61**
Animal species	**Chickens, turkeys, cattle**
Tolerance levels/tissues	**1.0 ppm liver/kidney** **0.5 ppm muscle** **8.0 ppm egg yolk** **4.0 ppm whole eggs**
Withdrawal period	*** See below**
Current residue methodology	
Type of determinative step	**Fluorometric**
Sensitivity	**0.05 ppm**
Validation	**None**
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	**None**
Metabolic studies	**Inadequate**
Total residue studies	**Limited data available**

Conclusions

Determinative method is not specific — subject to false positive results (buquinolate, decoquinate, nequinate, and zoalene interfere). Method also gives high control background levels approaching tolerance.

***Drug has a zero withdrawal time when fed alone. In practice, except when fed to laying hens, it is fed in combination with one of the arsenicals which has a 5-day withdrawal time. Tissue residues over tolerance are not likely.**

This drug ranks fourth in dollar volume sales. FDA should initiate method development and a subsequent monitoring program to look at residues in eggs/yolks.

Drug	Arsenicals Arsanilate sodium Roxarsone Carbarsone Arsanilic acid
Drug classification	Growth promotant
CFR Title 21 Regulation	558.60 558.530 558.120 558.62
Earliest approval date	
Animal species	Chickens, turkeys, swine
Tolerance levels/tissues	See 556.60
Withdrawal period	5 days
Current residue methodology	
Type of determinative step	Spectrophotometric
Sensitivity	
Validation	AOAC Collab Study
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	None
Metabolic studies	Inadequate
Total residue studies	None

Conclusions

Methodology is satisfactory for arsenic as residue. Currently, only concern is for arsenic - toxicity of remaining portion of molecule has not been ascertained.

Confirmatory methods such as atomic absorption are available for arsenic to sustain regulatory actions.

Drug	Bacitracin zinc Bacitracin methylene disalicylate
Drug classification	Antibacterial
CFR Title 21 Regulation	558.76, 78
Earliest approval date	1960's
Animal species	Cattle, chickens, swine, turkeys, quail, pheasants
Tolerance levels/tissues	0.5 ppm in all tissues, milk, eggs
Withdrawal period	None
Current residue methodology	
Type of determinative step	Microbiological
Sensitivity	.025 ppm
Validation	None
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	None
Metabolic studies	None
Total residue studies	None

Conclusions

Determinative procedure is a microbiological depletion method (NCAA publication - "Antibiotic Residues in Milk, Dairy Products and Animal Tissues: Methods, Reports,, and Protocols, Revised Oct 1968"). This method has not been subjected to validation, but has a quasi-official status due to wide usage. However, method lacks specificity and is only apparent or presumptive evidence.

Overdosing studies have shown this drug is not absorbed and no residues are indicated. Regulatory method is of low priority.

Drug	**Bambermycins**
Drug classification	**Antibacterial**
CFR Title 21 Regulation	**558.95**
Earliest approval date	**3/27/75**
Animal species	**Chickens, swine**
Tolerance levels/tissues	**No regulation (tolerance) currently available**
Withdrawal period	**None**
Current residue methodology	
Type of determinative step	**Microbiological (Agar well)**
Sensitivity	**0.5 ppm**
Validation	
Species/tissues	**Swine, liver/muscle**
Number of laboratories	**DEN/NCAA**
Date	**1974**
Confirmatory procedure	**1975 - TLC/bioautograph**
Metabolic studies	**Inadequate**
Total residue studies	**Inadequate**
Conclusions	

Determinative procedure is basically a microbiological depletion method.

The confirmatory bioautograph procedure was successfully validated in 1975 using dosed and spiked tissues at the 0.5 ppm level. This method lacks specificity since only one TLC solvent system is used.

Drug	Buquinolate
Drug classification	Antiprotozoal
CFR Title 21 Regulation	558.105
Earliest approval date	10/25/66
Animal species	Chickens
Tolerance levels/tissues	0.4ppm liver/kidney/skin(fat) 0.1 ppm muscle 0.2 ppm whole egg 0.5 ppm yolk of eggs
Withdrawal period	* See below
Current residue methodology	
Type of determinative step	Fluorometric
Sensitivity	
Validation	None
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	None
Metabolic studies	Inadequate
Total residue studies	Inadequate

Conclusions

Determinative method lacks specificity — cannot differentiate from other similar compounds (Decoquinate, Nequinate, Amprolium, Zoalene).

*Drug has a zero withdrawal time when fed alone. In practice, except when fed to laying hens, the drug is fed in combination with one of the arsenicals which have 5-day withdrawal periods. It is not likely a tissue residue over tolerance would be found.

This drug has not been recently marketed.

Drug	Carbadox
Drug classification	Antibacterial
CFR Title 21 Regulation	558.115
Earliest approval date	10/08/79
Animal species	Swine
Tolerance levels/tissues	No residue
Withdrawal period	10 weeks
Current residue methodology	
Type of determinative step	GLC -
Sensitivity	30 ppb
Validation	No dosed tissues - 1972
Species/tissues	Liver, muscle
Number of laboratories	BF/DEN
Date	1972, 1979
Confirmatory procedure	GLC/MS (validated in dosed tissues 1979)
Metabolic studies	Inadequate
Total residue studies	Inadequate
Conclusions	

Drug is a suspect carcinogen subject to NOOH.

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Drug	Chlormadinone Acetate
Drug classification	Estrus Synchronizer
CFR Title 21 Regulation	558.126
Earliest approval date	04/29/69
Animal species	Cattle
Tolerance levels/tissues	No residue
Withdrawal period	28 days
Current residue methodology	
Type of determinative step	GLC
Sensitivity	0.02 ppm
Validation	
Species/tissues	All tissues (spiked only)
Number of laboratories	KAN/BF
Date	1968
Confirmatory procedure	None
Metabolic studies	None
Total residue studies	None

Conclusions

In 1971, sponsor was requested to submit statement of intention regarding development of tissue assay methodology sensitive to 5 ppb level or provide toxicological data to support a higher sensitivity level.

Drug has limited usage — has not been marketed for at least the past four years.

Drug	Chlortetracycline
Drug classification	Antibacterial
CFR Title 21 Regulation	558.128, 145, 155
Earliest approval date	1950's
Animal species	Swine, cattle, poultry, ducks
Tolerance levels/tissues	See 556.150
Withdrawal period	See 558 regulations
Current residue methodology	
Type of determinative step	Microbiological
Sensitivity	.05 ppm
Validation	None
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	
Metabolic studies	Inadequate
Total residue studies	None

Conclusions

Determinative procedure is a microbiological depletion method (NCAA publication - "Antibiotic Residues in Milk, Dairy Products and Animal Tissues: Methods, Reports, and Protocol Revised Oct 1968"). This method has not been subjected to validation, but has a quasi-official status due to its wide usage. However, method lacks specificity and is only apparent or presumptive evidence.

A confirmatory TLC for the "cyclines" was unsuccessfully collaborated in 1978.

Drug	Clopidol
Drug classification	Antiprotozoal
CFR Title 21 Regulation	558.175
Earliest approval date	01/11/68
Animal species	Chickens, turkeys
Tolerance levels/tissues	See 556.160
Withdrawal period	* See below
Current residue methodology	
Type of determinative step	GLC
Sensitivity	0.1 ppm
Validation	AOAC Collab Study
Species/tissues	Muscle/liver
Number of laboratories	10
Date	
Confirmatory procedure	None available
Metabolic studies	Inadequate
Total residue studies	Inadequate

Conclusions

Determinative method is an Official First Action AOAC method. Method was also successfully validated by three government laboratories.

*Drug has zero withdrawal time when fed to chickens and 5-day period when fed to turkeys. Drug is often fed in combination with arsenicals which have 5-day withdrawal times.

Drug	Coumaphos
Drug classification	Anthelmintic
CFR Title 21 Regulation	558.185
Earliest approval date	05/09/68
Animal species	Cattle, chickens
Tolerance levels/tissues	1 ppm in tissue 0.5 ppm in milk
Withdrawal period	None
Current residue methodology	
Type of determinative step	Fluorometric
Sensitivity	0.1 ppm
Validation	
Species/tissues	Liver/muscle (spike only)
Number of laboratories	DAL
Date	1970
Confirmatory procedure	None
Metabolic studies	Inadequate
Total residue studies	None

Conclusions

Fluorometric method is non-specific and false positive results may be given.

Drug has zero withdrawal time.

Drug	Decoquinate
Drug classification	Coccidiostat
CFR Title 21 Regulation	558.195
Earliest approval date	02/06/70
Animal species	Chickens
Tolerance levels/tissues	Muscle 1.0 ppm All other tissues 2.0 ppm
Withdrawal period	* See below
Current residue methodology	
Type of determinative step	Fluorometric
Sensitivity	0.1 ppm
Validation	
Species/tissues	Muscle/liver (spiked tissues only)
Number of laboratories	SEA/BF
Date	1969
Confirmatory procedure	None
Metabolic studies	Inadequate
Total residue studies	Inadequate

Conclusions

Determinative method lacks specificity — cannot differentiate from other similar compounds (Buquinolate, Nequinate, Amprolium, Zoalene).

*Drug has a zero withdrawal time when fed alone. In practice, except when fed to laying hens, the drug is fed in combination with one of the arsenicals which have 5-day withdrawal periods. It is not likely a tissue residue over tolerance would be found.

Drug	**Dichlorvos**
Drug classification	**Pesticide** **Anthelmintic**
CFR Title 21 Regulation	**558.180**
Earliest approval date	**07/09/65**
Animal species	**Swine**
Tolerance levels/tissues	**0.1 ppm**
Withdrawal period	*** See below**
Current residue methodology	
Type of determinative step	**GLC (FPD)**
Sensitivity	**0.01 ppm**
Validation	**None**
Species/tissues	**No dosed tissue**
Number of laboratories	**USDA**
Date	
Confirmatory procedure	**None**
Metabolic studies	**Inadequate**
Total residue studies	**None**

Conclusions

Assay method is non-specific; however, potential confirmatory methods (GLC/MS) are available.

***Drug has zero withdrawal time based on overdosage studies.**

Drug	Diethylstilbestrol
Drug classification	
CFR Title 21 Regulation	558.225
Earliest approval date	
Animal species	
Tolerance levels/tissues	
Current residue methodology	
Type of determinative step	
Sensitivity	
Validation	
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	
Metabolic studies	
Total residue studies	
Conclusions	

Drug has been withdrawn from the market.

FDA modified Eli Lilly Procedure (Donohoe) available for monitoring DES residues in edible tissues.

Confirmation - GC-MS.

Drug	Dimetridazole
Drug classification	Antiprotozal
CFR Title 21 Regulation	558.240
Earliest approval date	01/21/64
Animal species	Turkey
Tolerance levels/tissues	Zero
Withdrawal period	5 days
Current residue methodology	
Type of determinative step	GLC
Sensitivity	2 ppb
Validation	
Species/tissues	Spiked tissue only (Muscle/liver)
Number of laboratories	BF/DEN/USDA
Date	1972
Confirmatory procedure	None available
Metabolic studies	Inadequate
Total residue studies	Inadequate

Conclusions

GLC method for parent at 2 ppb failed validation - background too high with respect to tolerance.

This drug is a suspect carcinogen. Total residue studies have been requested.

Drug	Erythromycin thiocyanate
Drug classification	Antibacterial
CFR Title 21 Regulation	558.248
Earliest approval date	1957
Animal species	Chickens, turkeys, swine,
Tolerance levels/tissues	0.1 ppm swine tissue 0.025 ppm eggs zero - turkey/cattle
Withdrawal period	See 558.248
Current residue methodology	
Type of determinative step	Microbiological
Sensitivity	0.1 - 0.25 ppm
Validation	None
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	None
Metabolic studies	None
Total residue studies	None

Conclusions

Determinative procedure is a microbiological depletion method (NCAA publication - "Antibiotic Residues in Milk, Dairy Products and Animal Tissues: Methods, Reports, and Protocols, Revised Oct 1968"). This method has not been validated, but has a quasi-official status due to wide usage. However, method lacks specificity since it cannot distinguish this drug from lincomycin and oleandomycin.

Drug	Ethopabate
Drug classification	Antiprotozoal
CFR Title 21 Regulation	558.58
Earliest approval date	01/21/63
Animal speices	Chickens
Tolerance levels/tissues	1.5 ppm liver/kidney 0.5 ppm muscle, skin/fat
Withdrawal period	None
Current residue methodology	
Type of determinative step	GLC
Sensitivity	50 ppb
Validation	None
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	None
Metabolic studies	Inadequate
Total residue studies	Inadequate
Conclusions	

NADA 13-461V (July 12, 1977) submitted for laying hens was not approved. ^{14}C studies show drug residues are dissipated rapidly. Confirmatory procedure is of low priority.

Drug	Famphur
Drug classification	Insecticide
CFR Title 21 Regulation	558.254
Earliest approval date	
Animal species	Cattle
Tolerance levels/tissues	0.1 ppm
Withdrawal period	See 558.254
Current residue methodology	–
Type of determinative step	GLC
Sensitivity	0.04 ppm
Validation	None
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	None
Metabolic studies	Inadequate
Total residue studies	Inadequate
Conclusions	

Sponsor was asked in 1977 to improve the analytical method for residues of drug and its major metabolite and to conduct a new residue depletion study.

Drug	Ferrous fumarate
Drug classification	
CFR Title 21 Regulation	558.258
Earliest approval date	
Animal species	
Tolerance levels/tissues	
Current residue methodology	
Type of determinative step	
Sensitivity	
Validation	
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	
Metabolic studies	
Total residue studies	
Conclusions	

Drug is not marketed.

Drug	Furazolidone
Drug classification	Antibacterial Antiprotozoal
CFR Title 21 Regulation	558.262
Earliest approval date	08/20/53
Animal species	Swine
Tolerance levels/tissues	Zero
Withdrawal period	None
Current Residue Methodology	
Type of determinative step	TLC(PMD)/GLC
Sensitivity	2 ppb
Validation	Failed validation of 3 laboratory study
Species/tissues	Recoveries below 50% in all tissues
Number of laboratories	
Date	Late 60's
Confirmatory procedure	None
Metabolic studies	Inadequate
Total residue studies	Inadequate

Conclusions

There currently exists no approved determinative or confirmatory method.

Drug is a suspect carcinogen and subject of NOOH [41 FR 19906-19921 (1976)].

Drug	Griseofulvin
Drug classification	
CFR Title 21 Regulation	558.266
Earliest approval date	
Animal species	
Tolerance levels/tissues	
Current residue methodology	
Type of determinative step	
Sensitivity	
Validation	
· Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	
Metabolic studies	
Total residue studies	
Conclusions	

Approved for use in non-food producing animals - chinchillas.

Drug	Hygromycin B
Drug classification	Anthelmintic
CFR Title 21 Regulation	558.274
Earliest approval date	08/57
Animal species	Chickens/swine
Tolerance levels/tissues	Zero
Withdrawal period	None
Current residue methodology	
Type of determinative step	Microbiological TLC/Bioautographic procedure
Sensitivity	15 ppb
Validation	
Species/tissues	
Number of laboratories	NCAA
Date	1972
Confirmatory procedure	
Metabolic studies	Inadequate
Total residue studies	None

Conclusions

Method is a microbiological and TLC separation depletion procedure. Method has not been validated - accepted on desk validation by NCAA. Method is basically the same as the method published in he JAOAC for Hygromycin B in eggs.

The specificity of the bioautograph method is lacking since only one TLC system is used.

Drug	Ipronidazole
Drug classification	Antiprotozal
CFR Title 21 Regulation	558.305
Earliest approval date	05/13/71
Animal species	Turkey
Tolerance levels/tissues	No residues
Withdrawal period	See 558.305
Current residue methodology	--
Type of determinative step	GLC
Sensitivity	2 ppb
Validation	
Species/tissues	Turkey/liver & muscle
Number of laboratories	BF/USDA
Date	1970
Confirmatory procedure	GLC/MS
Metabolic studies	Inadequate
Total residue studies	Inadequate

Conclusions

Determinative method is satisfactory. GLC/MS confirmatory method rejected by BF trial (1976) due to sensitivity problems and low recoveries.

Drug has high sales volume.

Drug is a suspect carcinogen subject to NOOH.

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Drug	Lasalocid sodium
Drug classification	Antibacterial
CFR Title 21 Regulation	558.311
Earliest approval date	1976
Animal species	Chickens
Tolerance levels/tissues	
Withdrawal period	3 days
Current residue methodology	
Type of determinative step	TLC/Bioautographic
Sensitivity	0.01 ppm
Validation	
Species/tissues	Chicken skin-fat
Number of laboratories	DEN/USDA/NCAA
Date	1976
Confirmatory procedure	Inadequate
Metabolic studies	Inadequate
Total residue studies	Adequate
Conclusions	

Method is a depletion microbiological and TLC bioautographic separation procedure with auxiliary hydrolytic step for supportive evidence. Sponsor submitted interference data showing separation from 8 other antibiotics. A second TLC solvent system is needed for specificity.

Drug	Levamisole
Drug classification	Anthelmintic
CFR Title 21 Regulation	558.315
Earliest approval date	08/18/69
Animal species	Cattle/sheep/swine
Tolerance levels/tissues	0.1 ppm tissues (not approved for dairy cattle)
Withdrawal period	See 558.315
Current residue methodology	–
Type of determinative step	Polarographic
Sensitivity	0.1 ppm
Validation	yes
Species/tissues	
Number of laboratories	BF/KAN/USDA
Date	1969
Confirmatory procedure	GLC/MS submitted '77
Metabolic studies	Inadequate
Total residue studies	None in cattle Inadequate for chickens

Conclusions

The polarographic validated determinative method is deficient. The peak sizes are too small by current standards and subject to false positives.

A GC/MS confirmatory method submitted in 1979 was unacceptable for validation since the method lacks sufficient specificity.

Also, suitability of methodology applies only if parent-molecule is acceptable for monitoring tissue residues.

Drug	Lincomycin
Drug classification	Antibacterial
CFR Title 21 Regulation	558.325
Earliest approval date	02/02/70
Animal species	Swine, chicken
Tolerance levels/tissues	0.1 ppm swine tissue 0.1 ppm chicken tissue 0.15 ppm in milk
Withdrawal period	6 days - swine
Current residue methodology	TLC/Bioautographic (Two solvent systems)
Type of determinative step	
Sensitivity	0.1 ppm
Validation	
Species/tissues	Swine (muscle, fat, kidney) - spiked & dosed
Number of laboratories	DEN/NCAA/USDA
Date	1976
Confirmatory procedure	
Metabolic studies	Inadequate
Total residue studies	Inadequate

Conclusions

Method is a depletion microbiological and TLC bioautographic separation procedure.

Drug	Melengesterol acetate
Drug classification	Growth promotant/hormone
CFR Title 21 Regulation	558.342
Earliest approval date	01/26/68
Animal species	Cattle (Heifer)
Tolerance levels/tissues	No residues
Withdrawal period	48 hours
Current residue methodology	—
Type of determinative step	GLC
Sensitivity	25 ppb - GLC FIO (1974) 10 ppb - GLC-EC (1976)
Validation	Yes
Species/tissues	All tissues - muscle, liver, kidney, fat - including dosed
Number of laboratories	USDA/BF/DEN
Date	Validated 74/76
Confirmatory procedure	GLC/MS
Metabolic studies	Inadequate
Total residue studies	Inadequate

Conclusions

New determinative method successfully validated at 10 ppb.

Drug is a suspect carcinogen (in mice) and subject to NOOH.

Drug	**Monensin**
Drug classification	**Antiprotozoal, growth promotant**
CFR Title 21 Regulation	**558.355**
Earliest approval date	**05/19/70**
Animal species	**Chickens & cattle**
Tolerance levels/tissues	**0.05 ppm chicken & cattle tissues**
Withdrawal period	**3 days - chicken** **None - cattle**
Current residue methodology	
Type of determinative step	**TLC/Bioautography**
Sensitivity	**0.05 ppm**
Validation	
Species/tissues	**Liver**
Number of laboratories	**DEN/USDA/NCAA**
Date	**1969, 1975**
Confirmatory procedure	**Inadequate**
Metabolic studies	**Inadequate**
Total residue studies	**Adequate**

Conclusions

Method is a microbiological and TLC separation depletion procedure. Specificity of the bioautograph method is lacking since only one TLC system is used.

Drug	Neomycin
Drug classification	Antibacterial
CFR Title 21 Regulation	558.15
Earliest approval date	03/21/58
Animal species	Chickens, turkey, cattle, sheep
Tolerance levels/tissues	0.25 ppm calf tissue
Withdrawal period	Not established
Current residue methodology	—
Type of determinative step	Microbiological assay
Sensitivity	0.6 - 1.2 ppm
Validation	None
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	None
Metabolic studies	Inadequate
Total residue studies	None

Conclusions

Determinative procedure is a microbiological depletion method (NCAA publication - "Antibiotic Residues in Milk, Dairy Products and Animal Tissues: Methods, Reports, and Protocols, Revised Oct 1968"). This method has not been subjected to validation, but has a quasi-official status due to wide usage. However, method provides only apparent or presumptive evidence since it cannot distinguish this drug from streptomycin or dihydrostreptomycin.

Drug is most commonly used in combination with oxytetracycline. Because of its wide usage, persistance of residues and potential for misuse, high priority should be given the development of adequate determinative and confirmatory methods.

Drug	Nequinate
Drug classification	Antiprotozoal
CFR Title 21 Regulation	558.365
Earliest approval date	05/20/71
Animal species	Chickens
Tolerance levels/tissues	0.1 ppm eggs, tissue
Withdrawal period	* See below
Current residue methodology	
Type of determinative step	Fluorometric
Sensitivy	0.1 ppm
Validation	
Species/tissues	
Number of laboratoriess	BLT/BF
Date	1971
Confirmatory procedure	None
Metabolic studies	None
Total residue studies	Inadequate
Conclusions	

Determinative method is not specific — it cannot differentiate from other similar compounds (Decoquinate, Buquinolate, Amprolium, Zoalene). Validation data indicate problems with "quenching" of the nequinate fluorescence due to impurities in the sample extracts.

*Drug has a zero withdrawal time when fed alone. In practice, except when fed to laying hens, the drug is fed in combination with one of the arsenicals which have 5-day withdrawal periods. It is not likely a tissue residue over tolerance would be found.

This drug has not been marketed since 1973.

Drug	Nicarbazin
Drug classification	Antiprotozoal
CFR Title 21 Regulation	558.366
Earliest approval date	10/04/54
Animal species	Chickens
Tolerance levels/tissues	4 ppm
Withdrawal period	4 days
Current residue methodology	
Type of determinative step	Polarography
Sensitivity	Acceptable at 2 ppm in muscle
Validation	
Species/tissues	Muscle, liver spiked & dosed (liver)
Number of laboratories	ATL/BF/USDA
Date	1973
Confirmatory procedure	None
Metabolic studies	Inadequate
Total residue studies	Inadequate

Conclusions

Determinative method satisfactory. Validation recoveries were $\geq$ 90%.

Drug has high dollar volume sales.

Drug	Niclosamide
Drug classification	
CFR Title 21 Regulation	558.367
Earliest approval date	
Animal species	
Tolerance levels/tissues	
Current residue methodology	
Type of determinative step	
Sensitivity	
Validation	
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	
Metabolic studies	
Total residue studies	
Conclusions	

Approved only for use in laboratory mice.

Drug	Nitrofurazone
Drug classification	Antibacterial
CFR Title 21 Regulation	558.370
Earliest approval date	01/12/48
Animal species	Chicken, turkey, swine
Tolerance levels/tissues	No published tolerance
Withdrawal period	None
Current residue methodology	
Type of determinative step	TLC(PMD)/GLC
Sensitivity	2 ppb
Validation	Failed validation in 3 laboratories
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	None
Metabolic studies	Inadequate
Total residue studies	Inadequate
Conclusions	

Determinative method failed validation trials. Recoveries were below 50% in all tissues at the 2 ppb level.

Drug is a suspect carcinogen and subject of NOOH [41 FR 19906-19921 (1976)], [41 FR 34899-34908 (1976)].

Drug	**Novobiocin**
Drug classification	**Antibacterial**
CFR Title 21 Regulation	**558.415**
Earliest approval date	**04/03/61**
Animal species	**Chickens, turkeys**
Tolerance levels/tissues	**zero**
Withdrawal period	**4 days**
Current residue methodology	**Microbiological**
Type of determinative step	**–**
Sensitivity	**0.1 ppm**
Validation	**None**
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	
Metabolic studies	**None**
Total residue studies	**None**

Conclusions

Determinative procedure is a microbiological depletion method (NCAA publication - "Antibiotic Residues in Milk, Dairy Products and Animal Tissues: Method, Reports, and Protocols, Revised Oct 1968"). This method has not been subjected to validation, but has a quasi-official status due to wide usage. However, method lacks sensitivity and specificity.

Drug	**Nystatin**
Drug classification	**Antifungal**
CFR Title 21 Regulation	**558.430**
Earliest approval date	**03/03/59**
Animal species	**Chicken/turkey**
Tolerance levels/tissues	**Zero**
Withdrawal period	**None**
Current residue methodology	
Type of determinative step	**Microbiological (Respirometric)**
Sensitivity	**4 ppm muscle/kidney 8 ppm skin/fat**
Validation	**None validated**
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	**None**
Metabolic studies	**None**
Total residue studies	**None**

Conclusions

Method has not been validated and lacks sufficient sensitivity for a zero tolerance.

Drug has a low sales volume.

Drug	**Oleandomycin**
Drug classification	**Antibacterial**
CFR Title 21 Regulation	**558.435**
Earliest approval date	**08/01/58**
Animal species	**Swine, chicken, turkey**
Tolerance levels/tissues	**.15 ppm**
Withdrawal period	**None**
Current residue methodology	
Type of determinative step	**Microbiological**
Sensitivity	**0.1 - 0.3 ppm**
Validation	**None**
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	
Metabolic studies	**None**
Total residue studies	**None**

Conclusions

Method is basically a microbiological depletion method which has not been validated. Method cannot distinguish residues from erythromycin and lincomycin.

Drug depletion studies have shown no detectable residues for a 10X overdose at zero withdrawal time. A regulatory method is, therefore, of low priority.

Drug has a low sales volume.

Drug	Ormetoprim
Drug classification	Antiprotozoal
CFR Title 21 Regulation	558.575
Earliest approval date	07/07/70
Animal species	Chickens, turkeys
Tolerance levels/tissues	0.1 ppm
Withdrawal period	See below *
Current residue methodology	
Type of determinative step	Fluorometric/TLC
Sensitivity	0.1 ppm
Validation	Yes
Species/tissues	
Number of laboratories	BLT/BF
Date	
Confirmatory procedure	None
Metabolic studies	Metabolites not studied
Total residue studies	Inadequate
Conclusions	

Fluorometric method is not specific. High control background levels approach tolerance.

*^{14}C-data indicates that tissues are well below 0.1 ppm 48 hours after withdrawal. Ormetoprim is only approved for use in combination with sulfadimethoxine which depletes slower. Residue programs should therefore monitor for sulfadimethoxine.

Drug	Oxytetracycline
Drug classification	Antibacterial
CFR Title 21 Regulation	558.450
Earliest approval date	1952
Animal species	Chicken, turkey, swine, cattle, sheep, fish
Tolerance levels/tissues	See 556,500
Withdrawal period	See 558.450
Current residue methodology	–
Type of determinative step	Microbiological
Sensitivity	0.1 ppm
Validation	None
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	None
Metabolic studies	Inadequate
Total residue studies	None
Conclusions	

Determinative procedure is a microbiological depletion method (NCAA publication -"Antibiotic Residues in Milk, Dairy Products and Animal Tissues: Methods, Reports, and Protocol Revised Oct 1968"). This method has not been subjected to validation, but has a quasi-official status due to its wide usage. However, method lacks specificity and is only apparent or presumptive evidence.

A confirmatory TLC for the "cyclines" was unsuccessfully collaborated in 1978.

Drug	Penicillin
Drug classification	Antibacterial
CFR Title 21 Regulation	558.145, 155, 460
Earliest approval date	
Animal species	Chicken, turkey, cattle, sheep, swine, quail, pheasant
Tolerance levels/tissues	
Withdrawal period	See 556.510
Current residue methodology	See 558.145, 155, 460
Type of determinative step	Microbiological assay
Sensitivity	0.01 ppm
Validation	
Species/tissues	Cattle/muscle, kidney, liver mammary (spiked & dosed)
Number of laboratories	DEN/NCAA/USDA
Date	1976
Confirmatory procedure	
Metabolic studies	Inadequate
Total residue studies	None

Conclusions

Microbiological method will not differentiate from other penicillin type antibiotics. Identification tests are available including a HPLC method for Benzathine Cloxacillin which was successfully validated in 1976. This method will differentiate "cillins".

Drug has high volume sales.

Drug	Poloxalene
Drug classification	Legume bloat preventative for cattle
CFR Title 21 Regulation	558.464, 465
Earliest approval date	08/14/68 - Feed premix
Animal species	Cattle
Tolerance levels/tissues	None established
Withdrawal period	None
Current residue methodology	Colorimetric
Type of determinative step	
Sensitivity	10 ppm
Validation	None
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	None
Metabolic studies	May not be needed
Total residue studies	None

Conclusions

Colorimetric determinative method is not specific. High control background levels obtained.

Poloxalene is probably not a residue problem due to poor absorption.

Drug	Pyrantel Tartrate
Drug classification	Anthelmintic
CFR Title 21 Regulation	558.485
Earliest approval date	03/27/75
Animal species	Swine
Tolerance levels/tissues	Kidney/liver 10 ppm Muscle 1 ppm
Withdrawal period	24 hours
Current residue methodology	–
Type of determinative step	GLC
Sensitivity	1 ppm muscle 10 ppm liver/kidney
Validation	Done on spiked tissues only
Species/tissues	Liver/kidney/muscle
Number of laboratories	DEN/USDA/BF
Date	1972
Confirmatory procedure	None available
Metabolic studies	Inadequate
Total residue studies	Inadequate

Conclusions

Drug is a suspect carcinogen.

Drug passed methods trial marginally; BF recommended re-evaluating data for use in swine.

Drug	Reserpine
Drug classification	Tranquilizer
CFR title 21 Regulation	558.505
Earliest approval date	07/21/59
Animal species	Turkeys
Tolerance levels/tissues	Zero for drug & metabolites
Withdrawal period	None
Current residue methodology	
Type of determinative step	Photofluorometric method
Sensitivity	Claimed 2 ppb
Validation	None
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	
Metabolic studies	Inadequate
Total residue studies	None
Conclusions	

Drug is a suspect carcinogen.

Drug has limited usage.

Drug	Robenidine HCl
Drug classification	Coccidostat
CFR Title 21 Regulation	558.515
Earliest approval date	09/73
Animal species	Chickens
Tolerance levels/tissues	0.2 ppm skin/fat 0.1 ppm muscle/liver/kidney
Withdrawal period	5 days
Current residue methodology	—
Type of determinative step	Polarographic
Sensitivity	0.1 ppm
Validation	Yes
Species/tissues	Liver & muscle only (spiked & dosed
Number of laboratories	BF/USDA/NYK
Date	1972
Confirmatory procedure	No
Metabolic studies	Inadequate
Total residue studies	Inadequate

Conclusions

In 1977 BF questioned adequacy of method. Validation done only on liver/muscle. Determination was made that target tissue should have been fat.

Drug	**Ronnel**
Drug classification	**Pesticide**
CFR Title 21 Regulation	**558.525, 526**
Earliest approval date	**10/24/57**
Animal species	**Cattle**
Tolerance levels/tissues	**10 ppm fat (cattle/goats/sheep)** **4 ppm tissue (cattle/goats/sheep)** **2 ppm fat (swine)**
Withdrawal period	**10 days**
Current residue methodology	
Type of determinative step	**GLC**
Sensitivity	**0.05 ppm**
Validation	**None**
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	**None**
Metabolic studies	**None**
Total residue studies	**None**

Conclusions

No official methods available.

AOAC or PAM-I pesticide multi-residue methods may be adaptable for tissue.

EPA has issued Presumptive Order that this drug is a potential carcinogen.

Drug	Streptomycin (Dihydrostreptomycin)
Drug classification	Antibacterial
CFR Title 21 Regulation	558.15
Earliest approval date	
Animal species	Chickens, turkeys, swine, cattle,
Tolerance levels/tissues	Zero
Withdrawal period	See 558.15
Current residue methodology	
Type of determinative step	Microbiological Assay
Sensitivity	1 ppm skin/fat 0.5 ppm muscle/liver/kidney
Validation	None
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	None
Metabolic studies	Inadequate
Total residue studies	None

Conclusions

Determinative procedure is a microbiological depletion method (NCAA publication - "Antibiotic Residues in Milk, Dairy Products and Animal Tissues: Methods, Reports, and Protocols, Revised Oct 1968"). This method has not been validated, but has a quasi-official status due to wide usage. However, assay lacks specificity since it cannot distinguish streptomycin and dihydrostreptomycin from neomycin.

Method also lacks sensitivity for a zero tolerance. Since this drug is widely used, development of adequate determinative and confirmatory methodology should be given high priority.

Drug	Styrylpyridinium chloride, diethylcarbamazine (as base)
Drug classification	
CFR Title 21 Regulation	558.565
Earliest approval date	
Animal species	
Tolerance levels/tissues	
Current residue methodology	
Type of determinative step	
Sensitivity	
Validation	
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	
Metabolic studies	
Total residue studies	
Conclusions	

Approved only for use in non-food producing animals — dogs.

Drug	Sulfonamides (General)
Drug classification	Antibacterial
CFR Title 21 Regulation	558.145, 155, 376, 575, 579, 582, 635
Earliest approval date	1940's
Animal species	Swine, cattle, poultry, goats turkeys, sheep, trout,rabbits
Tolerance levels/tissues	0.1 ppm
Withdrawal period	14 days - swine 7 days - all other species
Current residue methodology	Ion exchange or chromatographic extraction & Bratton-Marshall or modifications of Bratton-Marshall colorimetric procedure
Type of determinative step	
Sensitivity	0.1 ppm
Validation	Inadequate or none
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	None - See below for Sulfadimethoxine
Metabolic studies	None
Total residue studies	None

Conclusions

These colorimetric determinative methods are non-specific and subject to interferences and high background levels approaching tolerance.

Identity methods are needed for all sulfonamides. A GC/MS confirmatory procedure for sulfadimethoxine was submitted for trials in 1979. Based on initial data, method is in question. Validation requests were cancelled based on pending "Cyclic Review" for all sulfonamides.

A GLC method for sulfonamides is currently under review by BF.

Drug	Thiabendazole
Drug classification	Anthelmintic
CFR Title 21 Regulation	558.615
Earliest approval date	12/19/61
Animal species	Cattle, goats, sheep, swine
Tolerance levels/tissues	0.1 ppm 0.05 ppm milk
Withdrawal period	See 558.615
Current residue methodology	
Type of determinative step	Fluorometric
Sensitivity	
Validation	
Species/tissues	
Number of laboratories	3
Date	1964
Confirmatory procedure	None
Metabolic studies	Inadequate
Total residue studies	Inadequate

Conclusions

Method failed validation in two out of three laboratories. Other fluorescing substances may cause false positive results. GC/MS method submitted to BF in 1977 rejected because of inadequacies of the data supporting the drug.

Drug	Tylosin
Drug classification	Antibacterial
CFR Title 21 Regulations	558.625, 630
Earliest approval date	1962
Animal species	Swine, cattle, chickens, turkey
Tolerance levels/tissues	0.2 ppm
Withdrawal period	5 days - poultry None - cattle/swine
Current residue methodology	–
Type of determinative step	Microbiological assay
Sensitivity	0.1 ppm
Validation	None
Species/tissues	
Number of laboratories	
Date	
Confirmatory procedure	None
Metabolic studies	Inadequate
Total residue studies	None
Conclusions	

Determinative procedure is a microbiological depletion method. Method has not been validated and lacks specificity.

Drug	Virginiamycin
Drug classification	Antibacterial
CFR Title 21 Regulation	558.635
Earliest approval date	1975
Animal species	Swine
Tolerance levels/tissues	0.1 ppm tissues
Withdrawal period	None
Current residue methodology	
Type of determinative step	Microbiological
Sensitivity	0.05 ppm
Validation	
Species/tissues	Swine muscle/liver
Number of laboratories	NCAA only
Date	72/73
Confirmatory procedure	None
Metabolic studies	Inadequate
Total residue studies	Adequate
Conclusions	

Determinative procedure is a microbiological depletion method. The method was successfully validated by one laboratory. Method, however, lacks specificity and no identification of active agent is provided.

Drug	Zoalene
Drug classification	Antiprotozoal
CFR Title 21 Regulation	558.680
Earliest approval date	05/04/70 *
Animal species	Chickens, Turkeys
Tolerance levels/tissues	2-6 ppm dependent upon species and tissue
Withdrawal period	* See below
Current residue methodology	
Type of determinative step	Colorimetric
Sensitivity	1 ppm
Validation	AOAC Collab Study
Species/tissues	Chicken muscle
Number of laboratories	6
Date	1966
Confirmatory procedure	None
Metabolic	Inadequate
Total residue studies	Inadequate

Conclusions

Colorimetric method which determines parent and metabolite (3-ANOT) has AOAC Official Final Action status. Method, however, is non-specific and may give false positive results.

*Drug has zero withdrawal time when fed alone. In practice, except where fed to laying hens, drug is fed in combination with one of the arsenicals which have 5-day withdrawal periods. It is not likely residues over tolerance would be found.

Attachment I

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Dr. Sanford A. Miller
Director, Bureau of Foods (HFF-1)
Dr. Lester M. Crawford
Director, Bureau of Veterinary Medicine (HFV-1)

DATE: JUN 19 1979

FROM : FSQS(USDA)/FDA Work Group

SUBJECT: Assessment of Criteria Used in Evaluation of Microbiological Tests for Antibiotic Products

Attached is the FSQS(USDA)/FDA Work Group report on the criteria used in the evaluation of microbiological methods submitted for the analysis of antibiotic residues in edible products from food producing animals. Although this report is primarily concerned with antibiotics, you will note that we have also considered and made recommendations concerning the criteria for the evaluation of chemical or biological methods for other animal drug entities (non-carcinogenic types).

Very briefly, the Work Group is recommending that the criteria used in the evaluation of methods submitted for the analyses of animal drug residues be made uniform and that such criteria should follow those prescribed in the SOM document. As pointed out in this report the adoption of these criteria will not affect the review of chemical methods since, with the exception of the L_m, they are very similar to those currently employed. In contrast, it is believed that their adoption will tend to slow down the approval of new antibiotic products and along with the requirements for total residues may force the industry to turn to chemical methods. Regulated antibiotic products when subjected to cyclic review may be similarly affected. However, it is expected that microbiological tests will continue to be used as a screening tool if the selected marker residue (parent or metabolite) as determined by total residue studies contains the active component. Further, these tests along with suitable confirmatory procedures can be accepted as official methods if they can meet the total residue and aforementioned analytical criteria.

The Work Group recommends that the following actions be taken to upgrade the criteria used in the evaluation of methods of analysis for antibiotic residues in edible products from food producing animals:

Issue I

Criteria for the evaluation of methods of analysis for drug residues in edible products from food producing animals should be made uniform between the three Bureaus involved, i.e., BVM, BD and BF.

Approved ________________ Disapproved ______________ Date ________

Issue II

Criteria to be adopted should follow those outlined in the SOM document. These include the following attributes and criteria: dependability, practicability, specificity, accuracy and lowest limit of reliable measurement (i.e., the lowest limit of reliable measurement must be equal to or below the tolerance).

Approved ____________ Disapproved ____________ Date ____________

Issue III

The required analytical criteria for methods for the determination of noncarcinogenic animal drugs in edible products should be prepared by the three Bureaus involved and be included in the General Food Safety Guidelines currently in preparation.

Approved ____________ Disapproved ____________ Date ____________

Issue IV

Microbiological tests can be used for the analysis for antibiotic residues if the sponsor can conclusively demonstrate by total residue studies that the parent compound or its metabolite possessing microbiological activity can serve as an appropriate marker to monitor the total residue of toxicological concern. Such tests must meet the analytical criteria outlined in the SOM document with the exception that the lowest limit of reliable measurement must be equal to or below the tolerance.

Approved ____________ Disapproved ____________ Date ____________

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A

TYPES OF REGULATED ANTIBIOTIC FERMENTATION PRODUCTS

Antibiotic preparations for use in food producing animals are marketed as follows:

1. Natural products produced by bacterial or fungal fermentations -- the active ingredient(s) are marketed as:
    a. Purified or highly purified or crystalline product, or
    b. Unpurified mycelial cake or partially purified dried fermentation solids.
2. Semisynthetic products -- the active ingredient(s) is produced by chemical modification of a natural product (fermentation) precursor and is marketed in the highly purified state.

The attached list is a compilation of antibiotic drugs that have approved uses in food producing animals. Since most coccidiostats, anthelmintics, and antifungals are not classified as antibiotics by the CFR, these classes have not been included, though some are produced by fermentation. The sulfa drugs also have not been included.

The listing is made up of two groups: (1) antibiotics approved for use in feeds and (2) antibiotics not approved for use in feeds but which have other approved uses. Clearly, the antibiotics with the highest volume uses, particularly growth promotion, appear in the first group. Antibiotics in the second group have approved dosage forms as injectables, powders, suspensions, boluses, and topical and ophthalmic ointments. Some of these represent very low volume uses.

The following generalizations can be made about each group:

Group I - Approved for use in feeds

1. Most have growth promotion or feed efficiency claims as indicated in the attached listing.
2. Many also have therapeutic uses.
3. Many are listed in combinations with other drugs.
4. All are produced by fungal or bacterial fermentations.
5. Some are marketed as the mycelial cake; others are not. The Bureau of Veterinary Medicine is now making a study of this area.
6. All have microbiological assays for tissue residues. Assays for the content in feed may be chemical, spectrophotometric, or microbiological types.

Group II - Not approved for use in feeds

1. Many therapeutic uses and dosage forms are represented.
2. None have claims for growth promotion.
3. About half are produced by fermentation. The others are obtained by chemical modification of a precursor that was produced by fermentation.
4. None are marketed as the mycelial cake.
5. Many appear in approved drug combinations.
6. The approved uses of some indicate a very low volume product.
7. Most have a microbiological assay method for tissue residues.

ANTIBIOTICS WITH APPROVED NADAS

GROUP I. Approved for use in feeds.

Antibiotics	CFR Ref	Production Method	Weight Gain or Growth Promotion Claim (Species*)	Analytical Methods		High Market Volume (Species*)
				Feed	Tissues	
Bacitracin	558.76	Ferm	Chi, T, S, Cal	Micro	Micro	
Bambermycins	558.95	"	Chi, S	"	"	
Chlortetracycline	558.120	"	Chi, T, S, Ca	"	"	In top 10 Vet Drugs; Chi, S, Ca, Sh/G
Erythromycin	558.248	"	Chi, T, S, Ca	"	"	In top 10 Vet Drugs; T, Sh/G
Lasalocid	558.311	"	Chi	Spectro-fluorometric	Micro/TLC	
Lincomycin	558.325	"	S	Micro	Micro	
Monensin	558.355	"	Chi, Ca	Micro and Colorimetric	Micro/TLC	In top 10 Vet Drug; Chi, Ca
Neomycin	522.1484	"	None	Micro	Micro	Ca
Novobiocin	558.415	"	None	"	"	Chi, T
Nystatin	558.430	"	None	"	"	
Oleandomycin	558.435	"	Chi, T, S	"	"	
Oxytetracycline	558.435	"	Chi, T, S, Ca, Sh	"	"	In top 10 Vet Drugs; Chi, T, S
Penicillin G (Pen)	558.460	"	Chi, T, S	"	"	In top 10 Vet Drugs Ca, S/G
Pen/streptomycin	558.460	"	Chi, T,S	"	"	In top 10 Vet Drugs
Tylosin	558.625	"	Chi, S	"	"	In top 10 Vet Drugs
Virginiamycin	558.635	"	S	"	"	

ANTIBIOTICS WITH APPROVED NADAs

GROUP II. Not approved for use in feeds.

Antibiotic	CRF Ref	Production Method	Growth Promotion Claim	Analytical Methods (Tissues)	High Market Volume (Species*)
Amoxicillin	540.103	Semisyn	no	Micro/HPLC	
Ampicillin	540.105	"	no	Micro/Paper Chromatography	Ca
Cephapirin	522.365	"	Intramammary infusion only	Micro/HPLC	
Cloxacillin	540.014	"	" "	Micro/HPLC	
Dihydrostreptomycin	544.211	"	no	Micro	S, Ca, Sh/G
Gentamycin	522.104	Ferm	no	Micro	
Hetacillin	540.829	Semisyn	Intramammary infusion only	Micro/HPLC	
Polymyxin	544.170	Ferm	no	Micro	
Spectinomycin	522.2120	"	no	Micro	
Sulfomyxin	522.2340	"	no	Micro	
Tetracycline	546.180	Semisyn	no	Micro	Ca

*Chi=chicken, T=turkey, S=swine, Ca=Cattle, Sh/G=Sheep/goats; Cal=Calves

B

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Gary J. Dykstra, Compliance Coordination and Policy Staff, HFC-13 DATE: July 14, 1978

Karri Ridenour, Special Assistant to the Administrator, FSQS/USDA

FROM : FSQS/FDA Task Force

SUBJECT: Task Force Evaluation of Tissue Residue Methods

Attached is the ad hoc task force report of Residue Tissue Methodology as requested by you in your May 10, 1978 memo in preparation for discussion at the July 26, 1978 meeting between Dr. Kennedy (FDA) and Mrs. Foreman (USDA). Members of the Task Force included:

Food & Drug Administration

Dr. J. Howard, BF
Mr. T. Fazio, BF
Mr. J. Markus, BVM
Mr. F. Frappaolo, BVM

U. S. Department of Agriculture

Dr. R. Engel, FSQS
Dr. J. Spaulding, FSQS

The report is succinct and discusses the issues as the individuals know them. The conclusions are based on interviews, personal discussions and documentation made available to the group. Significant problems exist and must be resolved if an effective animal drug program is to be developed and maintained within each Agency.

The format is set up to bring to the attention of Dr. Kennedy and Mrs. Foreman the most pressing problem areas first, i.e., Agency policy is addressed followed by less policy and more technical discussions. The Task Force did not make recommendations because it felt that the problems were more in the realm of practicing policies and not at the technical level.

No executive summary is included because the Task Force felt that the problem areas were of such importance that Dr. Kennedy and Mrs. Foreman should be aware of the problems in their entirety.

Ronald E Engel John W Howard

Ronald E. Engel, Ph.D. John W. Howard, Ph.D.

Background

A Task Force comprised of FSQS(USDA) and FDA scientists recommended in their report on Tissue Residue Methods of July 14, 1978 that there was a need to assess the antibiotic area and develop policy with respect to the need for definitive criteria for microbiological tests. This recommendation was made after discussion with BVM, BD and FSQS personnel responsible for the validation of analytical procedures for antibiotic residues, who indicated that vastly different criteria are employed in the evaluation of these microbiological procedures as compared to chemical methods for other animal drug entities.

The BF Animal-Derived Food Safety Action Plan Proposal (7/18/78) also raised specific questions concerning microbiological tests and their regulatory applications:

1) Can microbiological tests function as regulatory methods and meet criteria adequate to sustain enforcement proceedings?

2) If so, what should these criteria be?

3) Can different standards for chemical vs. microbiological assays be supported?

The Action Plan Proposal recommended that a Work Group be established to evaluate the antibiotic area and prepare a report to the BVM and BF Directors. The need for such an assessment and development of criteria was stressed from the standpoint of the oncoming cyclic review. Accordingly a Work Group of FSQS(USDA), BVM, BD and BF scientists was convened at the request of the Program Manager for Animal-Derived Food Safety with the concurrence of the Directors of BVM and BF. Members of the Working Group were as follows:

U. S. Department of Agriculture

R. Johnston, FSQS
J. Spaulding, D.V.M., FSQS
R. Ellis, Ph.D., FSQS

Food and Drug Administration

F. Pugliese, BVM
R. Gryder, Ph.D., BF
T. Fazio, BF
J. Howard, Ph.D., BF
G. Carter, BD

The following attachments contain pertinent background information:

1) Types of Regulated Antibiotic Fermentation Products (Tab A).

2) FSQS(USDA)/FDA Task Force Evaluation on Tissue Residue Methods; memo and report to Ridenour (FSQS) and Dystra (FDA), 7/14/78 (Tab B).

3) Confirmatory Techniques for Veterinary Drugs; memo and report to Director, BVM from Director, Division of Chemistry and Physics, 4/6/76 (Tab C).

In its assessment the Work Group has included for your review a discussion of the following:

1) Requirements for NADA's for Antibiotic Products.

2) Responsibilities in the Assessment of Applications for Antibiotic Products.

3) Criteria Now Used in the Assessment of Microbiological Assays vs. Chemical Methods.

Requirements for NADA's for Antibiotic Products

It is important to note that antibiotic fermentation products for food producing animals have been regulated in the past somewhat differently than the non-antibiotic drugs produced by chemical synthesis. This has been due primarily to the fact that many of the initially proposed antibiotics for animals had prior use with a history of human drug therapy. Consequently, the Agency's policy was to utilize the aforementioned human experience information in their safety assessments and further requirements were generally not imposed with the exception of the submission of microbiological tests for the analysis of activity in the animal tissues. However, in recent years, there has been more concern about the presence of residues in the tissues other than those possessing microbiological activity. This concern can primarily be attributed to the expansion of classes of antibiotics and the introduction of more toxic antibiotics with little human use experience and longer residing residues. In addition, various reports have indicated that substantial portions of some antibiotics are inactivated in vivo: clindamycin [not regulated](1), lincomycin (2), some macrolides (3), and chlorotetracycline (4). The microbiologically inactive metabolites may or may not be of toxicogical concern, but their fate is not known unless total residue studies have been conducted.

As alluded to earlier, microbiological assays traditionally employed to determine antibiotic residues do not provide sufficient information since many antibiotics are at least partially metabolized to metabolites without microbiological activity. Accordingly, since 1975, there has been a trend in FDA to apply to antibiotic products many of the more stringent requirements applied to animal drugs prepared by chemical syntheses. This trend is evidenced by the current requirement that total residue studies for antibiotics be conducted to demonstrate the relationship between the microbiologically active residues and the total drug residues. This requirement was justified on the basis that a large body of safety data did not exist for these substances, many of which are structurally complex and unusual compounds. The factors involved in such evaluations include the toxicity of the product and the available information on its metabolism. More recently there has been concern that the fermentation biomass present in some of the aforementioned antibiotic products may contain some unidentified toxic factors and therefore, should be subject to a food safety evaluation. Guidelines for the aforementioned areas are currently under development by BF.

It should be pointed out that since the initiation of the total residue requirement for antibiotic products in 1975, various problems have been encountered by the industry in generating acceptable data. The majority of these problems are related to: (a) the inadequate radiolabeling of the active ingredients, (b) incomplete structure determination of the active ingredient, or (c) multiple active factors in the products.

Responsibilites in the Assessment of Applications for Antibiotic Products

As with other animal drugs BVM has the responsibility for evaluating the efficacy and the safety of an antibiotic product for administration to an animal. BVM is also responsible for the desk or paper review of the data submitted in support of microbiological methods for (a) the determination of antibiotic residues in edible products, i.e., tissues, milk, eggs, etc. and (b) the determination of antibiotics in medicated and contaminated animal feeds. The vast majority of methods submitted for the analyses for antibiotics have been microbiological zone inhibition tests. These tests which were originally designed for screening purposes are simple and rapid and a great number of samples can be processed in a short period of time. A major disadvantage is that only the portion of the residue(s) possessing microbiological activity is measured; inactive metabolites or degradation moieties split off from the active component in the animal body are not detected. During the last several years the industry has been including additional techniques to aid in the identification of a particular antibiotic, since the microbiological tests are generally lacking in specificity. These techniques include bioautographic TLC, fractionation by liquid chromatography and more recently an RIA procedure. The method trial of these tests is carried out by the Bureau of Drugs (BD), FSQS/USDA and Denver District Laboratory. There has been a long standing agreement between BVM and BD concerning the conduct of trials of microbiological methods.

BF has had limited involvement in the review of methodology in antibiotic submissions and does not comment unless specifically requested by BVM. These latter requests are usually concerned with the review of chemical methods proposed for antibiotic residues. This is in accordance with existing agreements between BVM/BF and BVM/BD. As will be discussed later in this report, there are marked differences in the criteria employed in the evaluation of the adequacy of microbiological tests as compared to those utilized for chemical methods. These differences can present problems when BF is requested to evaluate chemical procedures for an antibiotic product because of the imposition of more stringent criteria.

BF personnel have had the total responsibility for the review of toxicological data submitted in antibiotic applications and during the past several years (since 1975) have also assumed responsibility for an assessment of total residues as discussed in the previous section.

Criteria Used in the Assessment of Microbiological Assays and Chemical Methods

The Agency has operated on a more or less informal basis with respect to the criteria used in the evaluation of analytical methods submitted in part requirement for regulation of animal drugs. This lack of specific criteria has obviously had an untoward effect on the quality of the analytical methods that the Agency has available for the monitoring of animal drug residues in food products. It has also contributed to the use of vastly different criteria in the various Bureaus charged with the same responsibility, i.e., the review and assessment of analytical methods submitted in partial requirement for regulation of animal drugs.

Although not published, BF has been requiring for the past five or six years that chemical methods submitted by the drug sponsor meet various criteria with respect to dependability, practicability, specificity and accuracy. These criteria which encompass the requirements for average recovery value ranges, dosed (incurred) residue tissue data and confirmatory techniques discussed below were implemented on a gradual basis since no set criteria had been previously employed in the evaluation of these procedures. Thus, the majority of the chemical methods approved prior to 1972-1973 do not meet current day standards. BVM and BD in the review of microbiological tests submitted in support of antibiotic applications have employed more general and less stringent criteria since traditionally antibiotic products have been regulated on a different basis as mentioned in an earlier section of this report.

In 1977, the Agency attempted to take a positive step in outlining, among other requirements in the Sensitivity of Method (SOM) document, criteria for analytical methods for carcinogenic drug residues in the edible products from food producing animals. Subsequently, this document was remanded to the Agency for administrative procedural reasons, however, it has now been republished as a Proposal (Federal Register 44, #55, 17070-17114, 1979). The specified analytical requirements involve the following attributes and their criteria: dependability, practicability, specificity, accuracy and the lowest limit of reliable measurement (L_m). The procedure for determining the L_m lays down definitive criteria in that the method must be able to distinguish, with a high degree of confidence (99%) target tissues that contain levels of the marker residue (parent or metabolite) at or above the derived safe level (R_m) from target tissues that do not. This procedure has recently been tested by BF and its practical application to analytical methods has been found acceptable. Criteria for the aforementioned attributes can be readily applied to methods for non-carcinogenic drugs and with the exception of the L_m encompass those criteria currently employed by BF.

The main differences in criteria as currently employed by BVM, BD, and BF in the assessment of antibiotic and chemical assays are discussed in brief below:

1) Recovery data -- BVM does not impose specific criteria for recovery values in the evaluation of microbiological detection assays although most of the procedures submitted are designed for quantitation. Although not published, BF since 1972 had utilized the following guidelines for recovery values for example, at a 0.1 ppm level or above, average values should approximate 80-110% with a within laboratory coefficient of variation not exceeding 10%; at levels below 0.1 ppm, average values should approximate 60-110% with a within laboratory coefficient of variation not exceeding 20%.

2) Dosed tissue data -- BF requires that the industry submit these data along with recoveries to demonstrate that the extraction part of the chemical method is in fact capable of removing the biologically incurred residue (marker residue from the edible animal tissue, i.e., the target tissue). Such data are crucial in the evaluation of the practical application of the method. These studies are usually conducted by administering the labeled drug or metabolite to the animal followed by a time interval for the total drug residues to deplete in the target tissue to a level approximating the proposed tolerance. The marker residue is then extracted from the target tissue using the extraction solvent and technique employed in the proposed chemical method. Measurement of the radioactivity in the extract and the residual tissue is used to assess the effectiveness of the extraction technique. Exhaustive extraction techniques with the solvent prescribed in the method can also be employed on the target tissue. In the latter case the drug is administered without the radiolabel.

   Dosed tissue data are not requested by BVM to demonstrate the effectiveness of the extraction process in removing incurred residues of antibiotics from the animal tissue. Since the majority of these methods are quite simple and do not involve complex separation techniques, it would appear that the low recovery values obtained with some of the submitted methods may be due to initial ineffective extractions of the tissue matrix.

3) Confirmatory techniques -- BF has required the animal drug industry to submit confirmatory techniques to establish the identities of drug residues along with the determinative chemical methods since 1973-1974. The need for such techniques and a discussion of approaches to establishing identity of residues are summarized in Attachment C. In brief, it is pointed out that essentially all determinative chemical methods submitted for drugs in animal tissues (including gas (GC),

liquid (LC), thin layer chromatography (TLC), etc.] are non-specific and can best be described as "indicative" or subject to question with respect to identification of a particular residue. In particular such questions are concerned with the possible presence of other drug residues or closely related contaminants either naturally occurring in the tissue matrix or introduced via adsorbents, solvents, glassware, etc., which on occasion may be carried through the cleanup technique and may give the same Rf or Rt as the standard compound. For example, considerable problems have been experienced in the nitrosamine area where positives have been reported on the basis of GLC retention times, polarographic wave potentials, and Rf values using non-specific reagents on TLC plates. Follow-up investigations with mass spectrometry have demonstrated that these were indeed false positives.

In assessing the need for identification of pesticides at residue concentrations, Elgar (Advances in Chemistry Series No. 104, American Chemical Series, American Chemical Society, Washington, D. C., 1971) has stressed that measurement of similar physical property parameters (Rf, Rt values, etc.) either used alone or in combination may help in some cases to support identification but they are not the best means of doing so. This author also concluded that retention times in gas chromatographic analyses were often highly correlated and thus could not be depended upon to provide independent evidence of identity.

As noted above BVM has been requiring the industry during the past year to submit assays which would lend some support to the determinative microbiological test with respect to residue identification. These assays include bioautographic thin layer chromatography (TLC) or liquid chromatography (LC) which are used in combination with the zone inhibition technique. For example, with the TLC technique, aliquots of the tissue extract are applied to an adsorbent on a plate in the conventional manner The TLC plate is developed and then overlaid with a seeded agar layer, incubated overnight, and the inhibition zone used for the determination of the antibiotic. The calculated Rf value is employed for identification purposes. With respect to LC, aliquots of the tissue extracts are introduced to the column and the fraction collected at an established elution volume predetermined for the compound under analysis. The collected fraction is then subjected to a microbiological procedure.

Discussion

The Work Group first reviewed the current status of microbiological tests and their use by FSQS/USDA and FDA as a regulatory tool for the determination of antibiotic residues. These tests are ideal screening tools because they are simple and rapid and a great number of samples can be processed in a short period of time. On the other side of the coin, however, they measure only the portion of the compound(s) possessing microbiological activity; inactive metabolites or degradation moieties split off from the active component which may or may not be of toxicological concern are not detected. With the current requirement for accounting for the total residue it can be expected that the industry may have to shift from microbiological tests to chemical methods for some products which show longer residing inactive residues of toxicological significance in edible animal tissues. The same situation would also apply to approved antibiotics when subjected to cyclic review.

As found by the FSQS/USDA and FDA Task Force on their review of Tissue Residue Methods (7/14/78) there is a need for definitive analytical criteria for antibiotic products whether these be microbiological tests or chemical methods. It was the consensus of the Work Group that with the criteria currently employed for the evaluation of microbiological tests, both FSQS and BVM are in a very weak position to pursue enforcement action with respect to residue violations resulting from the use or administration of antibiotics to an animal. BVM and BD personnel on the Work Group and involved in the review of NADAs for antibiotics were emphatic in their response that they did not believe that data obtained with these tests could support follow-up action. They pointed out that over a nine year period only one prosecution case had been attempted and this was rejected by the General Counsel's office.

Based on the foregoing, the Work Group recommends that the criteria for the evaluation of methods for the analysis of drug residues in edible products from food producing animals should be made uniform between the three Bureaus involved, i.e., BVM, BD and BF. These analytical criteria should follow as closely as possible those outlined in the SOM document. It is also recommended that a document outlining the required criteria to be applied to all methods for non-carcinogenic animal drugs in edible products should be prepared by the three Bureaus involved and be included in the General Food Safety Guidelines. Such an upgrading would provide the support needed for enforcement purposes, and would clearly communicate our requirements to the regulated industry and the public.

Of lesser importance but still of significance to the review function, the Work Group recognized that uniform requirements would also eliminate problems in dealing with industry. For example, on at least one occasion when BF was asked to comment, difficulties were encountered in explaining the differences in the aforementioned criteria between the two Bureaus (BVM and BF) to the industry. This involved the review of an RIA method submitted by Schering Corporation as a confirmatory procedure for an antibiotic, the determinative method being the microbiological assay. BF concluded that at their present stage of development RIA methods could not be accepted as confirmatory procedures by themselves. This decision is supported by experts in the Field who have noted that the specificity of an RIA procedure should be checked with an established method. In the aforementioned case the submitted RIA assay was supported only by the microbiological test. The firm's representatives finally agreed to attempt the development of a LC procedure capable of separating the 3 major isomers of the antibiotic and which could be used in conjunction with the RIA test to provide a basis for confirmation of identity. However, they questioned the differences in criteria in the evaluations as employed by BVM and BF and pointed to other recently regulated antibiotics which had not been subjected to these more rigorous requirements. More recently the firm complained to the AVMA concerning the handling of the NADA. Although this is the only case that can be cited to date, the Work Group concluded that it is clear that the lack of uniform criteria between the various Bureaus involved in an assessment can present some problems from the standpoint of imposing differing requirements on the firms.

The Work Group has discussed at some length the feasibility of adopting the criteria outlined in the SOM document and its impact on the antibiotic area. It was the general consensus of the members of the Work Group with expertise in the area of microbiological tests that these tests probably would be able to meet the aforementioned average recovery value range of 80-110% at the 0.1 ppm and higher levels. However, it was noted that the majority of the available tests for regulated antibiotics would not meet this criterion at the present time. At levels below 0.1 ppm, it was stressed that microbiological procedures could not meet the specified average recovery value range of 60-110%. Work Group members noted that there had been little attempt to improve the limit of reliable measurement of these tests, since most of the tolerances for antibiotics had been set at the 0.1 ppm level or higher. A recent submission indicated, however, that cloxacillin residues could be detected at the 10 part per billion level using the microbiological test in conjunction with LC. As alluded to above, it was felt that the total residue requirement would tend to lower the derived safe level for the marker residue and with the adoption of the recovery and L_m criteria would tend to shift emphasis from microbiological to chemical methods.

With respect to dosed tissue data requirements, the industry would probably be forced to develop more elaborate extraction techniques to assure the removal of the antibiotic from the tissue or other edible product in quantitative yields. Most of the extraction techniques employed in current microbiological screening methods call for only one extraction or the slurrying of the matrix in aqueous media with subsequent application of an aliquot to inoculated agar substrate. As previously noted, ineffective extractions of the tissue matrix may be a major factor in the low recovery values obtained with many of the submitted tests. The Work Group was of the opinion that the complex structures of the antibiotics may limit the use of radiolabeling techniques with respect to the position of the label, however, exhaustive extraction using the solvent prescribed in the test can also be employed to obtain the necessary data.

The importance of having available adequate,confirmatory procedures was discussed in detail by the Work Group. Although BVM has requested the industry to submit additional procedures to give support to the zone inhibition tests, the procedures are not sufficiently rigorous to establish identity and sustain subsequent regulatory action. First and foremost, the determinative microbiological tests are lacking in specificity since they rely on activity measurements which may be subject to interference from other regulated antibiotics. As previously indicated, the LC and TLC procedures submitted thus far are used in combination with the microbiological tests. The Rf or elution volume values obtained, although presumptive or indicative, would not firmly establish the identity of a residue in a violative sample, since again other antibacterial residues might give the same values. Consideration can be given to follow-up inspections in an effort to establish that a particular antibiotic or drug was used by a producer; however, on most occasions this approach has not been productive.

The adoption of the criterion for confirmatory procedures would obviously force the industry to employ more sophisticated chemical approaches for the identification of the residue in question. Among others, these approaches would involve more detailed cleanup steps to isolate and purify the compound for confirmation. It was the consensus of the Work Group that the complex structures and mixtures of some antibiotic products could present special problems in the development of such techniques. Accordingly, it should be recognized that this requirement may affect the approval of some antibiotic products for which the sponsor may be unable to develop a suitable confirmatory techniques.

With respect to total residue requirements for antibiotic products, it was mentioned earlier that the industry has encountered various problems in completing such studies to BF's satisfaction. Since BF now has these problems under consideration, the Work Group would emphasize that there is a need for definitive metabolic information on all such products unless it can be established that the drug will not require monitoring because of a very high margin of safety. Without such data, the requirement for an analytical method or microbiological test becomes moot, since no assessment can be made as to the appropriateness of the marker residue in the monitoring of the total residue of toxicological concern. Thus, microbiological tests can be used for the analysis of antibiotic residues if the sponsor can conclusively demonstrate by total residue studies that the parent compound or its metabolite possessing microbiological activity can serve as an appropriate marker to monitor the total residue of toxicological concern. As previously mentioned, however, such tests must also meet the analytical criteria outlined in the SOM document.

As indicated throughout this report it can be expected that the adoption of the SOM analytical criteria will impact on the development of new antibiotic animal drugs. The application of very similar analytical criteria by BF has obviously impacted on other animal drug entities as evidenced by the fact that only five method trials have been carried out successfully from 1972 to the present. Using much less stringent criteria during the period of 1965-1971, over 20 animal drugs (other than antibiotics) were regulated. It should be stressed, however, that these comparisons must be tempered by the fact that other requirements for metabolic and toxicological data were implemented during the 1972-present period and have also affected the development and approval of non-antibiotic drugs.

Obviously, the logical question to be asked is, are the criteria too stringent? The Work Group does not believe that they are. With the exception of the L_m procedure the analytical criteria specified in the SOM document (including the requirements for average recovery ranges at the indicated levels, dosed tissue data and confirmatory techniques) have been employed by the Agency for a number of years with methods of analysis for pesticide residues and food additive alteration products. Without such criteria the requirement for an analytical method becomes a farce and both FSQS and FDA are left in an untenable position in that they will be unable to meet their responsibilities with respect to residue monitoring and subsequent enforcement.

References

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2. P. Ma, M. Lim and J. H. Nodine, "Human Pharmacological Studies of Lincomycin, a New Antibiotic for Gram-positive Organisms," Antimicrob. Ag. Chemother., p. 183 (1963).

3. L. P. Garrod, H. P. Lambert, F. O'Grady, Antibiotics and Chemotherapy, 4th Ed., Churchill Livingstone, London, p. 173 (1973).

4. A. Kucers and N. Mck. Bennett, The Use of Antibiotics, 2nd Ed. Wm. Heinermann Medical Books, Ltd., London, p. 393 (1975).

INTRODUCTION:

An ad hoc Task Force comprised of FSQS(USDA) and FDA scientists was established May 10, 1978 to examine the tissue residue analytical methodology as jointly employed by the two Agencies. No written specific instructions were given to the group. However, it was the consensus that the charge was to identify problems associated with the laboratory examination of tissues for residues and to recommend possible steps that might be taken to solve problems or improve operations in this area.

In order to properly understand the statutory authority of both Agencies and the impact upon the animal drug program, a short description of their respective responsibilities is presented below:

FDA

The FDA has the statutory authority to regulate the marketing of new animal drugs based upon a demonstration of their efficacy and safety. This includes the evaluation of the safety of the drugs to animals as well as the safety of food products derived from animals treated with the drugs and intended for human consumption. As part of the approval process, directions for use of the drug and methods of analysis for residues are prescribed. FDA is also responsible for enforcing proper usage of drugs and taking legal actions such as injunction and prosecution against offenders. It must rely on the residue monitoring activities conducted by FSQS(USDA) to identify violators.

FSQS (USDA)

The FSQS under its authority mandates must assure a safe meat and poultry supply for public consumption. To undertake such mandates, the Agency conducts a residue monitoring program which is predicated upon the availability of suitable methods of analysis. It follows that if excessive residues are uncovered by FSQS as the result of the residue monitoring program, the Agency under its law has the authority to retain any animals presented for inspection until the residue has depleted or require destruction of violative animal products. FSQS has "on the spot" regulatory authority.

While FSQS can take action on suspicion of adulteration, FDA must have unequivocal evidence of the violation for court action. The differences in the execution of each Agencies' programs has fostered differences in requirements for analytical methodology. FSQS's time requirements are far more stringent than FDA's due to the very short time frame they have to analyze for residues (approx. 24 hours) before the carcass must move into commercial channels. FDA's reliability requirements are far more stringent than FSQS's since in order to obtain supportable data for court action, accurate and specific methodology, which sometimes may require 3 or more days to run, must be utilized.

The Task Force recognized that a Joint FSQS (USDA)/FDA Committee on Analytical Methods for Animal Drug Residues has been in existence since 1974 to deal with problems in tissue residue analysis between the two Agencies. The members were of the opinion that it was important to assess the effectiveness of this Joint Committee in relation to the residue methodology, the problems it had encountered, the need for its continuance, and reorganization or disbandment. Such an assessment has been made and is discussed later in this report.

The Task Force believes that there are major problems that exist in the animal drug residue area which impact upon the effectiveness of the drug regulation program. This report will identify problems which involve both organizational and technical deficiencies. The following major issues are addressed:

1. Lack of a central control point for program direction within FDA.
2. Requirements for continued lower residue levels vs current and practical analytical capabilities.
3. Deficiencies in tissue residue methods.

PROBLEMS

Problem I. Lack of a Central Control Point for Program Direction Within FDA.

An effective organizational mechanism does not operate within FDA and therefore between FSQS and FDA. Within FDA, the animal drug program is the only regulatory program having routine responsibility for the same product divided between three Bureaus, i.e., the Bureau of Foods (BF), Bureau of Drugs (BD), and the Bureau of Veterinary Medicine (BVM). Briefly, BF is responsible for assuring the safety of the food supply; BVM is responsible for FDA's veterinary medical policy and compliance activities; and The National Center of Antibiotic Analysis in the Bureau of Drugs has responsibility for the validation of methods for antibiotic residues. In addition, EDRO, the Field Operational Bureau, is responsible for the Field investigational and laboratory operations. This division of responsibilities has in the past had a detrimental and often confusing impact on the operation of the animal drug program both within FDA and also between FSQS and FDA.

At the present time there appears to be a lack of direction and coordination in the use of methods in the regulatory and monitoring activities of both Agencies and even within different segments of the individual Agencies. Modifications have been made in official methods and in some cases the Agencies have employed entirely different methods to analyze the same samples. This has resulted in wide discrepancies in the data obtained and often renders results useless to both Agencies. Overall, an upgrading of the analytical methods used in these efforts is required. However, until such time as new methods are developed, the Agencies must continue to utilize the available methods as prescribed even though they may have some deficiencies with respect to meeting present FDA/FSQS criteria.

There is an immediate need to reevaluate the coordination and conduct of the drug residue effort as carried out by the two Agencies. In our view, no recommendations to date have gone far enough, particularly from the standpoint of establishing a central control point for the direction and coordination of a monitoring and compliance program, because they have not addressed the problems inherent in managing a program operated under fragmented authorities and responsibilities.

CONCLUSIONS:

1. The most important aspect of the animal drug program is the protection of the human food supply; therefore a central control point should be established in that part of the Agencies charged with that responsibility. Liaison between the two Agencies and the Agencies and the industry should also be the segments of the Agencies that are responsible for human food protection, i.e., BF and FSQS.

As an alternative, consideration could be given to the establishment of a central control point in the Commissioner's office, i.e., in the Office of the Associate Commissioner for Regulatory Compliance.

2. Formal involvement of both Agencies in the planning of monitoring/surveillance programs should be accomplished through a Memorandum of Understanding (MOU) in light of what is found the most desirable system of residue control.

3. Residue programs' credibility rest to a large degree on the capability and reliability of the analytical methods employed. Therefore, methods of analyses should be jointly agreed upon and used in the laboratories as prescribed. Agencies should have an ongoing program for study of and familiarization with each method and conduct continuing interlaboratory validation and quality assurance programs.

Problem II: Requirements for Continued Lower Residue Levels vs Current Practical Analytical Capabilities.

The Task Force feels that the continuing trend toward the requirements for lower tissue residue levels should be addressed. This issue should be examined very carefully by both Agencies because of its impact on the regulatory activities.

During the last several years there has been a trend toward the implementation of more stringent requirements for data to support the tissue residue methods. It is expected that lower residue levels and even more stringent data requirements will be proposed for carcinogenic residues in the near future. These requirements, for the most part, concerned with the determination of carcinogenic drug residues in animal tissues at part per billion (ppb) or part per trillion (ppt) levels, are such that an effective and reliable regulatory program will be extremely difficult to execute.

Although there has been notable advances in instrumental techniques to detect chemicals, there remains the very difficult problem of applying these analytical techniques to samples of biological material so as to reliably detect, measure, and confirm the presence of residues at these levels. The methods developed for these low levels are tedious and difficult, since they involve the isolation of minute quantities of the chemicals from complex tissue matrices. Obviously, vigorous pretesting by the industry should aid in the elimination of "bugs" in the method, but such testing cannot improve analyst variability. Furthermore, such testing will not guarantee that the procedure can be routinely and reliably used by our government monitoring and enforcement laboratories, particularly if the levels to be determinated are in ppb or the ppt range. The vast majority of such methods require the services of highly trained and experienced analysts. Since methods at the ppb or ppt levels are usually subject to numerous interferences (air, solvents, adsorbents, matrix, other residues, etc.), additional methods for confirmation of identity are required. At ppb levels, mass spectrometry (MS) is generally the confirmatory procedure of choice; at ppt levels, additional sophistication of analysts' skills and instrumentation are required. For example, MS has been used on one or two occasions (dioxins) for determining residues at the ppt levels, but in general the technology has not been developed beyond the research stage.

During the last several years considerable effort has been expended on the development of immunoassay techniques for determination of residues in tissues. These biological techniques, which possess some built-in specificity, have been used extensively in clinical laboratories for the analysis of body fluids. However, they have not been sufficiently developed or proven for tissue residue regulatory analysis.

To re-emphasize the point, most methods at the lower ppb levels cannot be used routinely in the regulatory activities of FSQS or FDA laboratories, or in any other laboratory for that matter, without developing and maintaining the requisite high level expertise. This statement applies not only to methods submitted to the Agencies by the industry but also to methods developed by the Agencies themselves. For example, the success of the two Agencies in the monitoring of carcinogens in foodstuffs such as aflatoxins (15 ppb or less in plant tissues) and polycyclic aromatic hydrocarbons (2 ppb or less in meat and fish) was achieved through extensive research in the simplification of the methodology, and workshops and specialized training of the personnel involved. Another outstanding example is the FDA multiresidue gas chromatography-mass spectrometric (GLC-MS) method for volatile N-nitrosamines currently used by both Agencies which seven years after its development and application can only be employed by a few industrial or academic laboratories for the accumulation of data.

All of the foregoing obviously impacts on the regulatory activities of the two Agencies. The major question to be addressed is whether we want to operate on the brink or beyond what can be practically and reliably achieved by the current analytical technology. As stated by Hirschfeld (Anal. Chem. 48, 16A-31A, 1976) in a recent feature article on the "Limits of Analysis," "The Delaney Amendment and other masterpieces of legal and bureaucratic regulation formally embody the principle of today's maximum analytical capability being tomorrow's minimal legal requirement. This automatic no-win situation for the developers of analytical techniques, besides its effects on the publication of analytical research, will keep a substantial fraction of the analytic workload in perpetual proximity to the technological and eventually fundamental limits."

CONCLUSIONS:

The Task Force believes that there is a need for a critical assessment of the continuing trend toward the requirement for lower tissue residue levels and its impact on regulatory activities. The Task Force also agrees that in theory the lower the residue level, the greater the protection afforded to public health. However, in actual practice the reverse is probably true. As levels are forced downward, methods become far more complex and unreliable with such untoward effects as: lengthy analysis time, decreased number of samples analyzed, increased sample and performance errors, difficulties in check analysis, a reduction in number of laboratories that can perform the analysis, and an increased potential for false positive and negative findings. All of these effects impact on the credibility of the Agencies' regulatory programs.

Problem III: Deficiencies in Tissue Residue Methods.

The Task Force has also reviewed the status of the available analytical methods for the determination of drug residues in animal tissues. At the present time there are approximately 100 active, parent chemical entities listed for direct use in animals for human food purposes. These entities include antibiotics, pesticides, and other chemical compounds including various hormones, sulfonamides, inorganics, and polymeric substances.

There are currently 79 marketed animal drugs for which specific tolerances have been published. This listing of drugs can be found in 21 CFR 556. Of this total, 34 drugs (43%) have methods that have been tested or validated either by method trial or under the auspices of the

AOAC. The above total of 34 is comprised of: 27 methods tested in one laboratory or more and 7 AOAC methods. It should be noted that a number of these latter methods may not meet modern day standards because of deficiencies in or lack of: recovery data, incurred residue studies and confirmatory techniques. In addition most of the methods have been developed for the parent drug which may or may not be of primary toxicological concern. Metabolism studies may reveal the need for the development of methods for significant metabolites.

Based on this review there are at least 45 drugs for which methods may or may not be available or the methods have not been tested. In those cases where methods are available it is doubtful if any of them would meet the present criteria for regulatory methods. Many of these method deficiencies can be attributed to the following:

- prior to 1958 regulatory analytical methods were not required of applicants;
- between 1958 and 1965 method requirements were based only on the potential for possible gross misuse of the drug or on the likelihood of residues occurring; and
- during 1965-71, residue methodology was required and tested on a selective basis at a FDA Headquarters laboratory; however, the criteria used in judging its acceptance were far below our present day standards.

The later part of 1971-1972 was a transition period during which changes were made in the criteria for acceptance of a regulatory method. Thereafter, laboratory trials of proposed regulatory methods became a routine requirement.

The cyclic review of animal drugs just getting underway in FDA should in time enable both Agencies to obtain methods for the determination of residues of individual drugs. Requiring the firms to submit methods for regulatory purposes as well as other pertinent toxicological and metabolic data will be a time consuming task. The availability of new or modified methods for individual drugs will most certainly strengthen both Agencies in carrying out their responsibilities. But, the Task Force is of the opinion that the monitoring of these drugs in edible tissues will still be limited by available resources. These limitations are concerned with the large number of drugs whose residues must be monitored on an individual basis. For example, FSQS(USDA) currently monitors for residues of 23 drug compounds on a yearly basis. This figure represents about 29% of the total number of drugs authorized for use with defined tolerances. This low percentage in part can be attributed to the inadequacies of available methods but the major reason is the lack of methods capable of analyzing a sample for several residues simultaneously, that is multiresidue methods. It was recognized a number of years ago that FDA could not effectively monitor the large number of pesticide residues with an individual method for each chemical. Accordingly, the Agency has devoted large resources in a continuing program to the development of multiresidue methods.

In assessing the animal drug program, it is obvious that neither Agency has expended substantive efforts to develop such capabilities in the drug residue area. The Task Force believes that both Agencies should make a commitment to the development of multiresidue approaches. Because

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of past neglect, this would require a substantial resource input to result in any significant advance in analytical methodology toward an operative residue monitoring program.

The Task Force believes that there is also a need for both Agencies to review the status of the microbiological assay procedures used for the determination of antibiotics in animal tissues. Discussion with BVM, BD, and FSQS personnel responsible for the validation of antibiotic procedures indicates that vastly different criteria are employed in the evaluation of these procedures as compared to the chemical methods for other animal drug entities. The Task Force has been advised that the more stringent criteria currently utilized for the evaluation of chemical methods could not be used in assessments of the microbiological tests. Further the imposition of the more stringent standards would force the industry to resort to specific chemical methods which may restrict the development of antibiotic products. Without strict analytical standards, regulatory action by FDA is difficult or impossible because of criminal evidence requirements. FSQS is in a slightly better position because it can take administrative action, since the presence of drug residues above an established tolerance cause the product to be adulterated. It is possible both Agencies are in a "Catch 22" position.

CONCLUSIONS:

The Task Force believes:

1. Both Agencies should make a commitment to develop multiresidue methods for drugs.

2. That there is a definite need to assess the antibiotic area and develop policy with respect to the need for definitive criteria.

TASK FORCE ASSESSMENT OF FSQS/FDA JOINT COMMITTEE ON ANALYTICAL METHODS

As indicated above the Task Force has also examined the activities of the FSQS/FDA Joint Committee on Analytical Methodology which was established by the two Agencies in 1974. The Task Force reviewed the Joint Committee's past experience and found that the most positivo accomplishment was an improvement in communications between the two Aguncies' technical staffs at the working level.

In reviewing the correspondence between the two Agencies concerning the proposed formation of the committee, there appears to have been a disagreement or confusion as to the "official" charge to the group. One Agency proposed that criteria should be developed for an acceptable retulatory analytical methods and this be used as the standard to evaluate all methods. This proposal was unacceptable to the other Agency which wanted each method reviewed on its merits. There was no written record made available to the Task Force to indicate that the matter was ever fully resolved or that clear written instructions were ever given to the committee.

The committee met on a bi-monthly basis. Minutes were taken and widely distributed to top administrative staff members of both Agencies. According to the committee's records, no formal comments on the committee's activities were ever received to give further guidance.

The committee chose to adopt an operational posture and attempted to correct deficiencies as they were encountered. Several projects which were of priority concern to both Agencies were accomplished or discussed, i.e., joint method evaluation for tetracyclines, DES, sulfonamide drugs, and chlorcmphenicol. The record of success for these

Projects was minimal and predictable because of the conditions under which the committee operated. There is no record that specific requests were made by the Joint Committee to the Agencies for assignment of resources for specific task accomplishment. Rather the members undertook to accomplish these tasks by utilizing resources under the members direct control in order to make as significant accomplishments as possible.

CONCLUSION:

The Task Force, at this time, does not believe the Joint Committee can be effective under current operating policies. The Task Force believes that the need for a committee should be evaluated and if deemed necessary be given a formal charge in harmony with a M.O.U. developed between the two Agencies.

Director, Bureau of Veterinary Medicine (HFV-1) April 6, 1976
Through: Associate Director for Sciences (HFF-100) ______

Director, Division of Chemistry & Physics (HFF-140)

Confirmatory Techniques for Veterinary Drugs

Attached is a draft of a report which summarizes our current thinking with respect to the subject area as discussed at one of the recent BVM/BF conferences. We would appreciate review by you and your staff for possible discussion at one of your meetings with Dr. Roberts in the near future.

John W. Howard, Ph.D.

Attachment

cc
HFF-1
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JWHoward:jds 4/6/76

CONFIRMATORY TECHNIQUES FOR VETERINARY DRUG RESIDUES

For the past several years the Division of Chemistry and Physics has been requesting manufacturers of animal drugs to provide confirmatory techniques along with the determinative method for residues of the drug in animal tissues. This requirement has generated considerable discussion within FDA and with APHIS/USDA about the need for such techniques. At a meeting of the Working Group on Veterinary Drugs, which included representatives from FDA and USDA, held May 23, 1975, the use of confirmatory methods was discussed in detail. Particular attention was given to the responsibilities of each agency in this regard.

At this meeting USDA representatives who are responsible for monitoring drug residues stated that the statute under which they operate provides authority to detain animals if evidence indicates that the carcass would be adulterated. The USDA must act quickly to prevent adulterated products from entering the market. Therefore they have concluded that confirmatory techniques in addition to their screening procedures are not required by their statute and that the use of these techniques would be burdensome, require more time, and cause delay in their actions. Provided the screening procedure has been demonstrated to meet the required level of detection, among other factors, they may elect to use all or only part of the officially approved method.

In summation it was agreed that USDA does not need to await confirmation of residues by FDA before proceeding with actions; however, APHIS/USD will continue to submit samples to FDA, since the latter agency has the responsibility for necessary follow-up regulatory action. If such action is contemplated, FDA will utilize both the official test method and appropriate confirmatory techniques to provide the necessary data. This agreement will form a part of "Policy Concepts Affecting Animal Drug Regulations" being developed by the Working Group; it is included here as background information for the following discussion on confirmatory techniques. Our objectives in presenting this discussion are primarily (1) to clarify further the need for confirmatory techniques, (2) to provide a basis for deciding when these techniques should be required, and (3) to review some of the approaches to establishing the identity of residues.

It is generally agreed that present toxicological standards and improvements in instrumental techniques have resulted in detection of lower residues levels. Thus the animal drug industry is required to develop more sensitive surveillance methods. Depending upon the residue level sought, the type of tissue sample to be analyzed and the properties of the compound to be determined, the complexity and length of these methods will vary. It is clear, however, that as residue levels become lower, cleanup procedures and elimination of interferences will become more difficult, and the possibilities of false positives will increase. Solvents, adsorbents or reagents used in the method, if not specially purified and tested, can cause spurious or false positive responses; the same is true of contaminated glass containers. The presence of unknown or unsuspected industrial pollutants can also cause serious analytical difficulties.

Essentially all determinative methods for determining drugs in animal tissues are nonspecific. The majority of these methods, except those for antibiotics, involve the use of gas chromatography, which at best provide only tentative identification of a residue. For example, analytical results obtained with a single gas chromatographic column and detector are questionable and should be regarded with caution. Widmark (Advances in Chemistry Series No. 104, American Chemical Society, Washington, D.C., 1971) has noted that gas chromatography is an excellent method for demonstrating that a known pesticide is not present at a given concentration, but it provides no positive information as to the identity of the compound that forms the peak. As Milton Schechter of USDA pointed out in an editorial in the Pesticide Monitoring Journal in 1968: "Data reported without application of suitable confirmatory techniques may not only be worthless, but what is worse, incorrect information may be seriously misleading and may be unrectifiable." This statement about pesticides applies even more appropriately to animal drug residues, which frequently must be determined at levels of a few parts per billion (and possibly in the future only parts per trillion) of carcinogens.

In a recent report on "Limits of Analysis" (Analytical Chemistry, 48 (No. 1), 16A, 1976), Hirschfeld stated: "Unless an analytical procedure also includes specific steps to confirm the identity of the analyte, there is always a finite (even if extremely small) probability of large errors which may or may not have the suspicious appearance that suggests a recheck. Furthermore, since such errors are systematic, replicates are no help." He pointed out that many of the early reports on the trace presence of DDT in nature were questionable and were later found to correspond to PCB's instead; thus a substantial fraction of the ensuing ecological panic was misdirected.

Based on these considerations, the regulatory chemist clearly needs confirmatory procedures to establish the identities of the residues in question if regulatory action is being contemplated. If industry does not supply such procedures, FDA will be forced to develop them as it has on past occasions (DES, Zearanol, and others).

As this Division now views the situation, two major questions must be addressed:

1. When will a confirmatory procedure be requested, and what are the exceptions to such requests?
2. What constitutes a confirmatory procedure?

FDA has devoted considerable discussion to what exceptions if any will be made in requiring the animal drug industry to provide confirmatory techniques. In 1974, an Ad Hoc committee of representatives from BF, BVM, and FDA's Denver District briefly discussed the need for confirmatory techniques. Their main charge, however, was to review the adequacy of available determinative methods for drug residues and make recommendations. Although this committee concurred that the ideal situation for regulatory purposes would be to have a specific method to identify each drug administered to food animals, they did not agree that such procedures are essential in every case. As the ensuing discussion shows, we agree with the latter statement.

As the Ad Hoc committee noted, various situations should be considered in determining the need for an identity test, as follows: the use of each drug; the withdrawal time required for each drug; the probability of illegal use; the available toxicity data; the use of a drug singly or in combination with a second drug that is depleted from tissues more slowly than the first and is therefore used as the indicator of residues; and the use of other drugs of similar chemical structure in the same species of animal. Thus a confirmatory test would not be required for drugs in which the identity of violative residues would never be a point of contention. Examples include drugs that do not require monitoring, i.e., they have been shown to require no withdrawal time because their only practical use is in week-old swine, day-old chicks, or cattle about to undergo minor surgery, or some similar use far removed from the time at which an animal might be slaughtered. A confirming assay would not be needed for drugs used only in combination with other slower depleting drugs (e.g., certain sulfonamide potentiators) and might not be required for drugs that would probably never be monitored because of a very high margin of safety or because the assigned tolerance levels are so high that any necessary identification of a violative residue would be a simple analytical problem.

In addition to the foregoing is the possibility of a method possessing inherent specificity. If the petitioner can provide firm evidence of this specificity, a confirmatory test would not be required. However, all of these situations must be evaluated for each individual drug.

Confirmatory procedures will be essential for those drugs deemed carcinogenic as well as those having toxicological significance and requiring ultrasensitive methods (in the ppb or ppt range) for their determination, as discussed above. We have also considered the need for confirmatory techniques for those drugs with tolerance levels above 0.1 ppm, and feel that, in general, an exemption for these latter drugs could be granted. This course is suggested because, if cleanup were adequate, the agency should be able to use modern instrumental techniques such as mass spectrometry to confirm the identity of a drug at levels above 0.1 ppm, if regulatory action is contemplated. However, such a waiver would depend on the evidence presented by the petitioner as well as the results of the method trial. For example, the reviewer should evaluate whether the chromatograms, spectra, and similar data obtained with the determinative methods are free of interfering background responses. If interfering peaks are present in or around the peak of interest or if control tissues show a positive response, a confirmatory assay will be required. Moreover the petitioner should provide data to demonstrate the absence of interference from other drugs, including related chemical types and drugs employed for different purposes in the same animal species.

Confirmation of residue identity is discussed in a general manner in Chapter IX of Guidelines on Analytical Methodology for Pesticide Residue Monitoring (June 1975). These Guidelines were compiled through the efforts of a committee of representatives from EPA, USDA, FDA and USDI. The general statement is made that "It is the responsibility of the analytical laboratory to support residue analyses with appropriate confirmatory work." In a more elaborate assessment, Elgar (Advances in Chemistry Series No. 104, American Chemical Society, Washington, D.C., 1971) has also reviewed the need to identify pesticides at residue concentrations. Both of these articles cover essentially the same area and emphasize the need for care in selecting confirmatory techniques. It is pointed out that, although combinations of confirmatory procedures that measure the same physical property or tests that measure the same parameters may help to support identification in some cases, they are not the best means of doing so.

Elgar's data emphasize the fact that Rf values in different paper chromatographic systems are not independent parameters, nor are Rf values in different TLC systems or extraction p-values in different pairs of solvents. The author adds that since the basis of separation for all three techniques is related to partition phenomena, it is not surprising to find that values for a compound obtained by all these techniques correlate to some extent. For example, studies were conducted with organochlorine insecticides in which Rf values by paper chromatography were compared to those obtained by TLC, and p-values were compared to Rf values obtained by TLC. The results indicate that although an Rf from TLC gives some additional evidence beyond the Rf from paper chromatography, the differen is not great and not worth the effort of using both methods. Similar results were obtained for the comparison between p-values and TLC.

Using GLC retention times on different column phases for positive co firmation of residues has also been evaluated. Thompson et al. (JAOAC, 52, 1263, 1969) compared retention times for Aldrin obtained with a nonpolar dimethyl siloxane polymer (DC-200) to those obtained with a highly polar DEGS phase. From these data and those obtained from a comparison of other stationary phases, Elgar concluded that the retention times were often highly correlated and thus could not be depended upon to provide independent evidence of identity.

It is true that techniques are available which depend on different physical behavior to achieve separation, i.e., paper chromatography depends on partition and GLC largely on vapor pressure. A comparison of data obtained by these two procedures and also by GLC supplemented with TLC indicates that paper chromatography and TLC support tentative identification by GLC. However, such identification can be open to question, especially in the parts per billion range with which we are chiefly concerned in this discussion. Such questions include the possible presence of closely related contaminants that either occur naturally in the tissue matrix or are introduced via adsorbents, solvents, glassware, etc., which occasionally may be carried through the cleanup and give the same retention time and Rf as the standard compound. For example, positiv values have been reported for nitrosamines on the basis of GLC retention times, polarographic wave potentials and Rf values obtained with nonspecific reagents on TLC plates; yet follow-up investigations with mass spectrometry have demonstrated that these were indeed false positives.

Both Elgar and the Guidelines for Pesticide Monitoring indicate that a battery of tests to substantiate identity can be considered in the absence of infrared spectrophotometric or mass spectrometric facilities.

TLC, p-values, element specific GLC, characteristic derivation are among the techniques noted. The use of such a battery, however, would depend on the compound being analyzed and the amount of sample available. The time element would also have to be evaluated in terms of its practicality. In this respect, the industry should be advised that we prefer that the confirmatory test be performed on the same extract as that used for the determinative method, if possible.

A review of petitions submitted for both food additives (packaging) and animal drugs during the past year reveal that firms are placing more emphasis on GLC/mass spectrometric techniques in meeting FDA requests for confirmatory tests at ppb levels. This trend is expected to continue because the technique can provide firm proof of identity even with low levels of a residue, and investigators working in the field realize the difficulty of attempting to develop alternative procedures for characterization in the ppb range. This is not to say that this Division will not consider other approaches. We have not, of course, considered all approaches; for example, if sufficient residue is available, infrared spectrometry can be used for identification with excellent results. Electron spin resonance (ESR) can be employed advantageously to detect and confirm low residue levels if the drug can be converted to a determinable species (charged radical), although the necessary instrumentation is not widely available in regulatory laboratories at this time and thus the technique might not be considered practical.

Cochrane, and Chau and Elgar (Advances in Chemistry No. 104, Americ Chemical Society, Washington, D. C. 1971) have reviewed the use of chemi derivatization of pesticides, followed by GLC, TLC, and other techniques, for this purpose in some detail; however, the specificity achieved must be carefully evaluated in terms of the structure of the compound and its derivative, and the likelihood that other regulated compounds may interfere with the proposed test. The same problems arise in evaluating hydrolytic or degradation products by chemical, photochemical, and other means in which the petitioner must furnish evidence to prove that the technique is in fact specific enough for the case in question. It then follows that the ability of each technique presented as a confirmatory procedure to identify the compound positively will have to be judged individually on the basis of the supporting evidence.

Question #11

The Committee to Analyze Presently Approved Detection Methods of Food Animal Feed Additives (the Andres Committee) recommended in its December 28, 1979, report that FDA initiate a drug residue monitoring program for milk. A March 31, 1980, analysis by Dr. Mukund R. Parkhie, Acting Special Assistant to the Associate Director for Human Food Safety, noted that while a number of drugs are approved for use in lactating dairy cattle, "milk is being monitored by state and local governments and creamaries for only penicillin group of antibiotics." Five years later, Dr. Joseph A. Settepani wrote in a March 20, 1985, memorandum that "we should have a regulatory program to monitor for residues in milk drugs such as flukicides that the states do not look for in their monitoring programs." What steps, if any, has FDA initiated to ensure monitoring of all animal drug residues left in milk?

Response

Responsibility for monitoring residues in milk rests with the Center for Food Safety and Applied Nutrition (CFSAN). However, CVM recognizes we have not adequately interacted with CFSAN regarding drug residues in milk. This issue was discussed with CVM's Field Committee at a meeting recently. It was decided that CVM will take the initiative to discuss the issue with CFSAN to ensure that their milk monitoring program gives appropriate attention to drug residues. Since the States have intensive monitoring program of milk for antibiotics (and some sulfas as well), CFSAN's milk program has focused primarily on pesticide and industrial chemical residues. We agree that drugs other than antibiotics and sulfas should also be taken into account, and that responsibility will likely fall upon the FDA rather than the States.

Question #12

On July 12, 1985, Dr. Judith Hauswirth, a CVM toxicologist, advised the subcommittee staff that CVM's Cancer Assessment Committee concluded that ipronidazole was associated with an increase in malignant lung tumors in mice. The CAC was requested to conduct such a review in a June 21, 1983, Division of Toxicology memorandum. When did the CAC conduct its last meeting on the drug? Why has no memorandum been prepared of the CAC's findings and conclusions?

Response

The Cancer Assessment Committee (CAC) met in August-September of 1983 concerning ipronidazole and it was decided to request historical control tumor data from the firm pertaining to the mouse chronic study. It was also decided to have the Biometrics staff calculate a virtually safe level for the drug from tumor data generated in both rodent bioassays. A CAC memorandum was not written at this time since additional data was needed to reach a definitive conclusion regarding the potential carcinogenicity of the drug. Also, it has been the policy of the CAC to only write memoranda containing final or definitive conclusions on a drug. Memoranda are generally not prepared containing interim judgments when additional toxicological data are needed. The CAC is presently awaiting additional data from within the Center in order to convene another CAC meeting and to provide final scientific judgment on ipronidazole.

Question #13

Has FDA calculated the "safe" levels for ipronidazole and dimetridazole corresponding to a cancer risk of 1 cancer in 1 million population, and, if so, please state what those levels are and when and by whom they were computed.

Response

Safe levels were calculated for ipronidazole by the Division of Mathematics, Bureau of Foods, in June 1978. They recommended the use of an estimate of tumor incidence somewhere between 72-84 weeks into the study, or 2.2 parts per billion (ppb) - 3.8 ppb using the one-hit model and 23 - 53 ppb using the Mantel-Bryan model.

Safe levels were also calculated for dimetridazole by the Division of Mathematics again in June 1978. Using the Mantel-Bryan model the safe dose was calculated to be 57 ppb and 2.9 ppb using the one-hit model.

Neither the Mantel-Bryan nor the one-hit model is considered any longer by the Agency to be the appropriate method for calculating a safe level of residues of concern. The Agency now accepts a linear extrapolation procedure.

Question #14

Dr. Crawford testified that CVM has taken steps to assure safe uses of ipronidazole and dimetridazole by requesting the sponsoring drug firms to develop acceptable detection methods. When did FDA ask these firms to develop detection methods capable of detecting residues at the "safe" level corresponding to a cancer risk of 1 cancer in 1 million population? Please supply copies of any and all agency requests for the development of such methods.

Response

We have discussed the safety issue of the drugs with the respective sponsor, but FDA has not requested the sponsors to develop methods for ipronidazole and dimetridazole at the "safe" level corresponding to a cancer risk of 1 cancer in 1 million population.

Question #15

Dr. Crawford testified that at the insistence of some 27 different groups, including consumer groups, attending a September 1983 meeting, CVM modified the policy announced on August 1, 1983, that prohibited all extra-label uses of drugs given to food-producing animals. Please list all consumer groups participating in this meeting.

Response

The groups present at the September 27, 1983 meeting are those listed in the attached news release.

News

FDA Rejects Extra-Label Drug Use Proposal

The extra-label use of drugs in food animals was the subject of a workshop held September 27 at AVMA headquarters. The meeting was arranged in response to concerns expressed by veterinarians that a new policy developed by the Bureau of Veterinary Medicine imposes excessive restrictions on extra-label use of food animal drugs.

At a September 1 meeting in Rockville, Md, BVM Director Lester M. Crawford had called for interested groups to join together in developing proposals for meaningful changes in the new policy. He invited the major practice-oriented veterinary groups to form a coalition to draft a policy that reconciles the practice of veterinary medicine with public health and the law.

Members of several practitioner and producer groups joined Dr. Crawford and AVMA staff members at the September 27 workshop to discuss revision of the policy which was announced in July 1983. The purpose of the workshop was to assist the Food and Drug Administration in developing an alternative policy that would not interfere with veterinarians' ability to provide adequate health care and would not restrict BVM officials in prosecuting individuals who misuse or illegally distribute food animal drugs. Participants agreed on a draft that would, if approved, serve both needs.

Among the organizers represented at the meeting were the American Association of Bovine Practitioners, American Association of Sheep and Goat Practitioners, American Association of Swine Practitioners, Academy of Veterinary Consultants, American Veal Producers, Livestock Conservation Institute, National Cattlemen's Association, National Milk Producers Federation, National Pork Producers Council, National Wool Growers Association, Professional Veterinary Products, AVMA Council on Biologic and Therapeutic Agents, AVMA Drug Availability Committee, AVMA Executive Board, and Bureau of Veterinary Medicine.

If the alternative policy were adopted, FDA authorities would still take necessary action in the case of drug misuse, but practitioners would, in the presence of an acceptable veterinarian-client-patient relationship, prescribe drugs for extra-label uses when, in their professional judgment, such use is in the animals' best interest. Since FDA failed to adopt the recommendations, veterinarians may be forced to practice under conditions of excessive legal jeopardy when they prescribe or use a drug for purposes other than those stated on the label.

The proposed policy as drafted on September 27 would have FDA agree that a veterinarian may use any drug in the course of professional practice that he/she may legally obtain, so long as there is the assumption by the veterinarian and client of responsibility for adverse reactions or drug residues in food animal products. It would also have FDA refrain from interfering in the normal course of professional veterinary practice, but FDA would take necessary action to prevent, stay, or curb the distribution and use of drugs not approved for food animal use in the absence of a veterinarian-client-patient relationship.

With respect to client-patient relationships, the conferees suggested these guidelines:

"A prescription veterinary drug cannot be safely used except under the supervision of a licensed veterinarian because of the drug's potential harmful effects or the method of its use. Thus the phrase "for use in the course of his/her professional practice" necessarily implies that the veterinarian is supervising the use of the prescription drug.

"In order for the veterinarian to supervise the use of a prescription drug or drugs not approved for food animal use, an appropriate veterinarian-client-patient relationship must exist.

"An appropriate veterinarian-client-patient relationship will exist when:

"(1) The veterinarian has assumed the responsibility for making medical judgments regarding the health of the animal(s) and the need for medical treatment, and the client (owner or other caretaker) has agreed to this role for the veterinarian; and when

"(2) There is sufficient knowledge of the animal(s) by the veterinarian to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s). This means that the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of an examination of the animal(s), and/or by visits from time to time to the premises where the animals are kept."

The September 27, 1983, workshop alternative proposals were subsequently supported by the AVMA Council on Biologic and Therapeutic Agents and Drug Availability Committee, but an October 5 letter from Dr. Crawford indicated that FDA would not support the modified position statement developed at the workshop. Consequently, the July restrictions announced by FDA continue to remain in effect.

Question #16

What are the levels of carbadox and its metabolites corresponding to a cancer risk of 1 cancer in 1 million population, and when did FDA calculate these levels? Has FDA requested the sponsor to develop an analytical method sufficiently sensitive to detect such levels, and, if so, when?

Response

FDA has never calculated a level of residue corresponding to a risk of one in one million, because the drug was approved prior to this criteria being established. Therefore, there has been no request for new analytical methodology.

Question #17

Dr. Crawford testified that some medicated blocks are being marketed that "are in the process of obtaining approval." Please identify all medicated blocks that are not the subject of an approved new animal drug application,, and state the legal basis for permitting their continued marketing.

Response

We previously provided this information in a response immediately following the hearing. As to the legal basis for continued marketing, please see Mr. Drozen's followup response.

Question #18

There are approximately 200 unapproved sulfa drugs currently being marketed. On July 22, 1974, FDA permitted these "new animal drugs" to be marketed without new drug approval if their sponsors submitted additional safety data. On July 5, 1984, FDA noted that few of these sponsors had submitted the data needed to ensure safe sulfa residue levels in edible products. On what legal basis has FDA now given these firms more than eleven years to market these new animal drugs without pre-market approval?

Response

The Agency has pursued and continues to pursue a conclusion to the interim marketing of medicated blocks and sulfa drugs. The interim use of sulfonamide drugs has been subject to the provisions of Title 21, Code of Federal Regulations (CFR) section 510.450. This section was established as a basis for requiring the submission of data on sulfonamide drugs in current use. To be eligible for continued marketing, firms were required to submit the results of 90-day subacute toxicity studies so that the Agency could determine the method sensitivity that would be required to show no drug residues in depletion studies. Firms failing to submit the required data were denied further interim marketing. In the Federal Register of July 5, 1984, a comprehensive notice was published outlining the total data requirements for approval of these products under current standards. An initial date of October 7, 1985, was set for submission of the required data and information following which, the Agency would take steps to revoke 21 CFR 510.450. Following revocation of the section, only those products for which approval had been granted could continue marketing. Steps to implement the final stages of this regulation are being developed.

For additional information regarding FDA's legal basis for permitting the continued marketing of sulfa drugs see Mr. Drozen's followup response.

Question #19

It is our understanding that the Animal Health Institute (AHI) has contracted to conduct the residue depletion studies needed to determine whether many unapproved new sulfa drug products can be approved. Have the protocols for these studies been submitted for FDA's review and, if so, when? Does FDA plan to initiate action to remove these drugs from the market if these studies are not submitted to the agency by October 7, 1985, the interim marketing termination date established by FDA in the July 5, 1984, Federal Register?

Response

It has been the stated intent of AHI representatives to perform cooperative studies in partial fulfillment of the requirements set forth in the Federal Register on July 5, 1984 (49 FR 27543). It must be understood that AHI's role is one of study coordination, that is, the study data are the property of the several companies sponsoring the research, and may be used by FDA/CVM to support pending and subsequent applications only as directed by each of the sponsoring companies.

Attached to an AHI letter dated July 11, 1985, were two proposed protocols entitled: (1) Tissue Residue and Bioavailability Study with Sulfamethazine Oral Liquid in Cattle, and (2) Tissue Residue and Bioavailability Study with a Triple Sulfa Combination Oral Liquid in Cattle. CVM responded to the July 11, 1985 letter on August 5, 1985, by telecon. An AHI letter dated August 29, 1985, (receipt dated September 6, 1985 by CVM's Mail Room) acknowledges this discussion of the protocols, and indicates that AHI agreed to make the suggested changes and forward the revised protocols shortly. No revised protocols have been reviewed in CVM as of October 7, 1985.

The Agency intends to follow the course of action outlined in the Federal Register of July 5, 1984. That is, after the Agency has reviewed each new animal drug application (NADA) covered by 21 CFR 510.450, they will either approve it or publish a notice of opportunity for hearing on denial of approval. Hearings will be held if justified. After a final rule revoking 21 CFR 510.450 becomes effective, any sulfonamide-containing drug on the market intended for use in food-producing animals which is not covered by an approved NADA will be subject to regulatory action.

Question #20

During an August 7, 1980, meeting, FDA's General Counsel stated that a 1977 proposal to permit interim marketing of unapproved teat dip products could not be finalized because the Federal court's decision in the Cutler v. Kennedy case rendered interim marketing arrangements illegal. Accordingly, as stated in a March 3, 1981, memorandum from Dr. Terence Harvey, then BVM's Deputy Director, the interim marketing proposal for teat dips was vacated. Why has FDA not similarly rescinded the interim marketing privileges it has granted for unapproved medicated blocks and sulfa drugs?

Response

The Agency has pursued and continues to pursue a conclusion to the interim marketing of medicated blocks and sulfa drugs.

Medicated Blocks

On August 2, 1976, FDA published a notice in the Federal Register (41 FR 32215) stating that all medicated blocks are subject to the new animal drug approval requirements. This notice was codified in Title 21, Code of Federal Regulations, section 510.455. Timeframes were established for the submission and approval of NADAs. Those times were extended by a second Federal Register notice on February 22, 1980 (45 FR 11800).

Only three drugs, EDDI, phenothiazine, and chlortetracycline, are currently involved in the interim use, as follows:

> No NADAs for EDDI blocks have been found to be approvable by CVM. In order to allow for an orderly phaseout of EDDI blocks, the following schedule was established:
>
> 1. No EDDI blocks may be manufactured after November 1, 1982;
> 2. No EDDI blocks may be distributed after December 31, 1982; and
> 3. No existing stocks at the retail level on December 31, 1982, may be sold until the stock is depleted.
>
> Phenothiazine has a history of use as an anthelmintic in animals. Those firms marketing the block under interim provisions have been permitted to continue to do so provided the firms have updated their applications with respect to manufacturing and labeling pending the Agency's final decision regarding the data to be submitted regarding human food safety. No new phenothiazine blocks have been permitted.
>
> With respect to chlortetracycline, there are no approved or permitted uses for chlortetracycline in medicated blocks.

Sulfonamide Drugs

The interim use of sulfonamide drugs has been subject to the provisions of 21 CFR 510.450. This section was established as a basis for requiring the submission of data on the sulfonamide drugs in current use. To be eligible for continued marketing, firms were required to submit the results of 90-day subacute toxicity studies so that the Agency could determine the method sensitivity that would be required to show no drug residues in depletion studies. Firms failing to submit the required data were denied further interim marketing. In the Federal Register of July 5, 1984, a comprehensive notice was published outlining the total data requirements for approval of these products under current standards. An initial date of October 7, 1985 was set for submission of the required data and information following which, the Agency would take steps to revoke 21 CFR 510.450. Following revocation of the section, only those products for which approval had been granted could continue marketing. Steps to implement the final stages of this regulation are being developed.

FOOD AND DRUG ADMINISTRATION
COMPLIANCE POLICY GUIDES

GUIDE 7125.30

CHAPTER 25 - VETERINARY DRUGS

SUBJECT: Teat Dips and Udder Washes for Dairy Cows and Goats

BACKGROUND:

A. Teat Dips

Teat dips are drugs that are applied to the teats of lactating animals immediately following milking and removal of the milking machine to control the spread of mastitis. Since the control of mastitis is inherent in the purpose for using teat dips, the control of mastitis constitutes their intended use whether or not specifically labeled for this purpose. In the FEDERAL REGISTER of August 9, 1977, (42 FR 40217) the agency published a proposed regulation which would designate teat dips as new animal drugs and require them to be subject to approved NADAs. The proposed regulation has not been finalized. The comments submitted in response to the proposal and other factors have resulted in a reevaluation of the intended regulation. This Guide establishes agency policy pending final disposition of the proposed regulation.

B. Udder Washes

There are many products being marketed which are intended and labeled for cleansing the udders of lactating cows and goats prior to milking. Use of these products is consistent with the Grade "A" Pasteurized Milk Ordinance (1965 Recommendation of the United States Public Health Service) which includes the following statements:

> The udders and teats of all milking cows shall be cleaned and treated with a sanitizing solution just prior to the time of milking, and shall be relatively dry before milking.

Udder washes may be classified as animal drugs if formulated to contain one or more antimicrobial chemicals as active ingredients, and labeling includes claims for controlling mastitis or the spread of mastitis, or labeling includes other claims for controlling microorganisms in or on the animal.

POLICY:

Teat dips and udder washes classified as drugs, may currently be marketed without NADA approval. AT some future time, these drug products may be required to comply with the NADA approval requirements of Section 512 of the Act.

Udder wash products promoted as cleansing agents and not classified as drugs could be required to be the subject of food additive regulations unless they are considered GRAS. This decision will be made on individual products based on directions for use and potential to contaminate milk and dairy products.

We do not expect to take regulatory action against teat dip and udder wash drug products on a 501(a)(5) charge unless we have specific information that a partiular product may be harmful, or ineffective. The Bureau of Veterinary Medicine will continue to review the labeling all teat dip and udder wash products and provide comment on their regulatory status and appropriateness of the labeling.

Manufactureres of teat dips and udder washes falling within the drug definition, are subject to the registration and drug listing requirements of Section 510 of the Act. Part 211 of the GMP regulations is applicable to the manufacture of teat dips and drug udder washes.

Ted Heiman — while this is filed & cancelled the — want to check up on its status?

Linda [illegible]
4/26/8[illegible]

[illegible]

VET

Acting Director, BVM, HFV-1 March 3, 1981

Deputy Director, BVM, HFV-2

Teat Dip F.R. Notice - Executive Order 12291

On March 2, 1981, I met with Ms. April, Mr. Geyer, Mr. Stribling, Mr. Grunk, Drs. Crandall, Scarr, Beaulieu, Carnevale, and Jacobs to discuss the status of the August, 1977 proposal to codify our position that teat dips are new animal drugs requiring an approved NADA. This proposal included an interim marketing provision for these products.

In view of the Cutler decision and other points including lack of enforcement action on this stance for those teat dip products for which no adverse information is available, we collectively concluded that the teat dip proposal should be vacated. The Bureau believes that teat dips are in fact new animal drugs; however, they as a product class, do not warrant attempting to pursue codifying our position by this or any other regulation.

Instead, I recommend that we prepare a Compliance policy Guide indicating that such products will be dealt with on a case-by-case basis. Furthermore, regulatory action may be deferred unless a product is shown to present a clear and present danger to public health. This approach is necessary to utilize our resources for more pressing regulatory needs and relegate teat dips to a lower compliance priority. A like CPG is in preparation for udder washes. After CPG finalization we could publish their availability.

Additionally, in conjuction with Executive Order No. 12291, Federal Regulation, I recommend the teat dip proposal be vacated under this directive and Secretary Schweiker's instructions of February 19, 1981, as it is the most expedient route. I am aware that other Bureau proposals will have to be addressed under this order but the teat dip proposal should be one of the first to go.

Terence Harvey, D.V.M.

cc: Dr. Crandall, HFV-2[illegible]
Dr. Scarr, HFV-214
Mr. Stribling, OCF-1
Ms. April, OCF-1 ✓
THarvey/[illegible]/3/3/81

then in its possession, or under its control, including claims for any funds unpaid or property not delivered at the time of such termination.

(b) The said trustees shall: (1) Continue in such capacity until discharged by the Secretary; (2) from time to time account for all receipts and disbursements and deliver all property on hand, together with all books and records of the committee and of the trustees, to such persons as the Secretary may direct; and (3) upon the request of the Secretary, execute such assignments or other instruments necessary or appropriate to vest in such person, full title and right to all of the funds, property, and claims vested in the committee of the trustees pursuant thereto.

(c) Any person to whom funds, property, or claims have been transferred or delivered, pursuant to this section, shall be subject to the same obligation imposed upon the committee and upon the trustees.

§—.65 Effect of termination or amendment.

Unless otherwise expressly provided by the Secretary, the termination of this part or of any regulation issued pursuant to this part, or the issuance of any amendment to either thereof, shall not (a) affect or waive any right, duty, obligation, or liability which shall have arisen or which may thereafter arise in connection with any provision of this part or any regulation issued under this part, or (b) release or extinguish any violation of this part or of any regulation issued under this part, or (c) affect or impair any rights or remedies of the Secretary or of any other person with respect to any such violation.

§—.66 Duration of immunities.

The benefits, privileges, and immunities conferred upon any person by virtue of this part shall cease upon its termination, except with respect to acts done under and during the existence of this part.

§—.67 Agents.

The Secretary may, by designation in writing, name any officer or employee of the United States, or name any agency or division in the United States Department of Agriculture, to act as the Secretary's agent or representative in connection with any of the provisions of this part.

§—.68 Derogation.

Nothing contained in this part is, or shall be construed to be, in derogation or in modification of the rights of the Secretary or of the United States (a) to exercise any powers granted by the act or otherwise, or (b) in accordance with such powers, to act in the premises whenever such action is deemed advisable.

§—.69 Personal liability.

No member or alternate member of the committee and no employee or agent of the committee shall be held personally responsible, either individually or jointly with others, in any way whatsoever, to any person for errors in judgment, mistakes, or other acts, either of commission or omission, as such member, alternate, employee or agent, except for acts of dishonesty, willful misconduct, or gross negligence.

§—.70 Separability.

If any provision of this part is declared invalid or the applicability thereof to any person, circumstance, or thing is held invalid, the validity of the remainder of this part or the applicability thereof to any other person, circumstance, or thing shall not be affected thereby.

***§—.71 Counterparts.**

This agreement may be executed in multiple counterparts and when one counterpart is signed by the Secretary, all such counterparts shall constitute, when taken together, one and the same instrument as if all signatures were contained in one original.

***§—.72 Additional parties.**

After the effective date thereof, any handler may become a party to this agreement if a counterpart is executed by him or her and delivered to the Secretary. This agreement shall take effect as to such new contracting party at the time such counterpart is delivered to the Secretary, and the benefits, privileges and immunities conferred by this agreement shall then be effective as to such new contracting party.

***§—.73 Order with marketing agreement.**

Each signatory hereby requests the Secretary to issue, pursuant to the act, an order providing for regulating the handling of kiwifruit in the same manner as is provided for in this agreement.

Copies of this recommended decision may be obtained from: William J. Doyle, Room 2532-S, U.S. Department of Agriculture, Washington, D.C. 20250, (202) 447-5975 or William Blackburn, P.O. Box 214297, Sacramento, California 95821, (916) 484-4855.

Signed at Washington, D.C., on June 28, 1984.

William T. Manley,

Deputy Administrator, Marketing Program Operations.

[FR Doc. 84-17732 Filed 7-3-84; 8:45 am]

BILLING CODE 3410-02-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 510

[Docket No. 84N-0036]

Notice to Sponsors of Drugs Containing Sulfamethazine, Sulfaquinoxaline, Sulfamerazine, Sulfathiazole, Sulfapyridine, or Sulfanilamide for Oral, Injectable, Intramammary, or Intrauterine Use in Food-Producing Animals; Termination of Interim Marketing; Data Submission Requirements

AGENCY: Food and Drug Administration.

ACTION: Notice of intent.

SUMMARY: The Food and Drug Administration (FDA) is announcing plans for the termination of interim marketing under § 510.450 (21 CFR 510.450) for drugs containing sulfamethazine, sulfaquinoxaline, sulfamerazine, sulfathiazole, sulfapyridine, or sulfanilamide for oral, injectable, intramammary, or intrauterine use in food-producing animals. FDA requests that sponsors of new animal drug applications (NADA's) covered by interim marketing submit a statement of intent with regard to continued marketing of their products and that sponsors submit data, revised labeling, and other information necessary for approval of an NADA. After evaluation of the information with respect to each NADA, FDA will either approve the NADA or publish a notice of opportunity for hearing on denial of approval. FDA will also publish at that time a proposal to revoke § 510.450.

This notice lists firms that have submitted NADA's for sulfonamide-containing drugs under the provisions of § 510.450 and sets forth data to be submitted for approval of NADA's, together with suggested label revisions for such products.

This notice also provides guidance to persons who wish to submit NADA's for the marketing of drugs containing these six sulfonamides for oral, injectable, intramammary, or intrauterine use in food-producing animals. Such NADA's

must be approved unconditionally before marketing may begin.

DATE: Sponsors must submit a letter of intent by October 3, 1984 and data, revised labeling, and other information by October 7, 1985.

ADDRESS: Submission to the Center for Veterinary Medicine (formerly Bureau of Veterinary Medicine) (HFV-133), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Charles Haines, Center for Veterinary Medicine (HFV 133), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3410.

SUPPLEMENTARY INFORMATION:

I. Background Information and Scope of This Notice

Section 510.450 was initially promulgated as § 135.102 (21 CFR 135.102) in the Federal Register of October 23, 1970 (35 FR 16536). The regulation established as an interim measure a 5-day withdrawal period for poultry and a 10-day withdrawal period for all other food-producing animals. The regulation applied to all sulfonamide-containing drugs for use in food-producing animals and required sponsors of NADA's for sulfonamide products to submit within 1 year (by October 22, 1971) residue depletion information to permit, based on such data, the establishment of appropriate withdrawal periods. FDA promulgated the regulation because new information available to the agency indicated that sulfonamide drug residues may be present in edible tissues of food-producing animals slaughtered within 10 days of the last treatment.

In the **Federal Register** of July 22, 1974 (39 FR 26033), FDA revised the regulation and deemed all sulfonamide drugs to be new animal drugs for which approved NADA's are required. Firms then marketing products containing sulfonamide drugs that were not the subject of approved NADA's were permitted to continue marketing the products on an interim basis, provided they submitted NADA's by January 20, 1975, and made a commitment to conduct and submit the results of 90-day feeding studies (toxicity studies) in a rodent and nonrodent species. Sponsors who did not meet the January 20, 1975 deadline have not been permitted interim marketing privileges.

FDA required the feeding studies because of concerns about thyroid toxicity. In addition, sponsors were required to develop more specific and sensitive regulatory methodology for detecting sulfonamide residues if existing methodology were found to be inadequate to monitor the tolerances for residues established following evaluation of those feeding studies. The results of those feeding studies were to be submitted by July 22, 1975. This date was extended to October 22, 1978 (September 19, 1975; 40 FR 43213). The feeding studies and the new methodology were to be submitted by sponsors of approved NADA's that had not already submitted such information as well as by those who had been given interim marketing privileges.

In the **Federal Register** of May 5, 1978 (43 FR 19385), FDA further revised the regulation to add the requirement that products containing sulfamethazine intended for use in swine feed or drinking water be labeled with a 15-day withdrawal time.

In the **Federal Register** of January 28, 1983 (48 FR 3962), FDA amended § 510.450 to require a 10-day withdrawal period for all sulfonamides for all animal species (except for the 15-day withdrawal for sulfamethazine used in swine feed or drinking water), unless a specific withdrawal period, based on data submitted and found satisfactory, had been established. FDA stated that it would reconsider the 10- or 15-day withdrawal times as part of the agency's evaluation of the human food safety of sulfonamides.

By January 20, 1975, 28 firms had submitted 229 NADA's requesting interim marketing under § 510.450. At present 190 NADA's cover interim marketing of sulfonamide products under § 510.450; the remaining NADA's were either withdrawn by their sponsors, or terminated by FDA for failure to submit required data.

This notice describes the requirements that must be met before FDA will give unconditional approval to the interim-marketing NADA's. These requirements also apply to persons who wish to submit NADA's for the marketing of these sulfonamides for identical claims. Finally, this notice discusses the status of the NADA's that were approved before the adoption of § 510.450.

Although § 510.450 included within its scope all sulfonamide-containing drugs, interim-marketing NADA's included products containing only six sulfonamides: sulfamethazine, sulfaquinoxaline, sulfamerazine, sulfathiazole, sulfapyridine, and sulfanilamide. Sponsors of NADA's submitted in the future for identical claims for these sulfonamides for oral, injectable, intramammary, or intrauterine use must meet the requirements stated in this notice. Sulfonamides other than these six are not within the scope of this notice. NADA's for other marketed sulfonamides have been approved unconditionally and are in full compliance with the human food safety requirements of § 510.450.

Of the six sulfonamides listed above, there are several unconditionally approved NADA's for currently marketed sulfamethazine and sulfaquinoxaline products. All approved NADA's for sulfamethazine as the sole drug are in full compliance with the requirements stated in this notice, including labeling claims. Approved sulfaquinoxaline products are in compliance with § 510.450 except for some human food safety requirements. FDA is working with the sponsors of those products to satisfy remaining data requirements. The data must be submitted not later than 18 months from the date of this notice.

II. Human Food Safety

Section 510.450 established three requirements concerning human food safety data: (1) Residue depletion studies, (2) 90-day subchronic toxicity studies (feeding studies), and (3) a regulatory methodology capable of monitoring residues at the established tolerance.

The effect of sulfonamide drugs on the thyroid was the major human safety concern. Based primarily on a published study on the effect of sulfamethoxazole on the thyroid (Ref. 1) and summaries of data included as proprietary information in NADA's, FDA concluded that the degree of thyroid response to exposure to sulfonamide drugs should be an important criterion in the evaluation of sulfonamide toxicity and the establishment of "no-effect" levels. Consequently, all sulfonamide drug sponsors were required to submit for each drug the results of 90-day subchronic toxicity studies in one rodent and one nonrodent species, which were adequate to support a tolerance for negligible residues.

The required toxicity studies were submitted on behalf of sponsors of all 190 NADA's for sulfonamide compounds currently marketed under § 510.450, and sponsors with previous approvals. With the exception of sulfaquinoxaline, the toxicity data support a tolerance of 100 parts per billion (ppb) (0.1 part per million (ppm)) for residues. The data for sulfaquinoxaline support a tolerance of 25 ppb (0.025 ppm). These data are proprietary. Sponsors of NADA's submitted in the future must either have authority to reference the appropriate master file containing the data or submit original data.

Residue depletion data for each species have been submitted for only a few of the 190 NADA's pending under § 510.450. These data, which are necessary to permit the assignment of preslaughter withdrawal periods that will ensure that edible products are free of above-tolerance sulfonamide residues, must be submitted for each NADA and must be collected by using a regulatory method reliable at least to the tolerance for residues for the drug in question. The Bratton-Marshall method or modifications to that method traditionally have been used to collect residue depletion data for sulfonamide residues in tissue. The agency will continue to accept data collected with this methodology, provided the data are supported by adequate recoveries of sulfonamides added to tissues under study. The results with the Tishler-A method (Ref. 2) appear to be slightly more reliable than those obtained by other modified Bratton-Marshall methods, at least for sulfamethazine, sulfathiazole, and sulfaquionoxaline. For determination of sulfamethazine the gas chromatography/mass spectrometric (GC/MS) assay developed by the U.S. Department of Agriculture (USDA) (Ref. 3) and the GC method of Manuel and Steller (Ref. 4) have been studied collaboratively in FDA and USDA laboratories and found to be acceptable (Ref. 5).

In 1979, FDA reevaluated its requirement for the confirmatory test for the Bratton-Marshall method and concluded that it would be wasteful for each sponsor to develop its own confirmatory test. The agency will complete the development of a standard mass spectrometry based confirmatory procedure.

The human food safety requirements for these interim marketed sulfonamide drugs do not reflect current approval standards. As discussed in section III below, the sulfonamide products covered by this notice are within the scope of the National Academy of Sciences/National Research Council (NAS/NRC) Drug Efficacy Study Implementation (DESI) program. (The DESI program only covered effectiveness and safety to the target animal.) FDA has in the past not required the sponsors of drug products that are identical or similar to DESI-reviewed products to meet current human food safety standards.

The human food safety requirements stated above apply to interim-marketed sulfonamide products for the DESI-reviewed claims listed in section VII below. These requirements also apply to sponsors of future NADA's for these six sulfonamide products with DESI-reviewed claims. Sponsors of interim marketing and future NADA's with different claims will be required to meet the current human food safety requirements. In the alternative, such sponsors may request hearings on denial of approval.

References

The following information has been placed in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, and may be seen by interested persons from 9 a.m. to 4 p.m., Monday through Friday.

1. "Observations on the Thyroid Gland in Rats Following the Administration of Sulfamethoxazole and Trimethoprim." *Toxicology and Applied Pharmacology*, 24:351-363, 1973.

2. Tishler, F., J. L. Sutter, J. N. Bathnish, and H. E. Hagman, *Journal of Agricultural and Food Chemistry*, 16:50-53, 1968.

3. Suhre, F., R. Simpson, and J. Shafer, *Journal of Agricultural and Food Chemistry*, 29:727, 1981.

4. Manuel, F. J., and W. A. Steller, *Journal of Association of Official Analytical Chemists*, 64:794, 1981.

5. Malanoski, A. J., C. J. Barnes, and T. Fazio, *Journal of Association of Official Analytical Chemists*, 64:1386, 1981.

III. Safety of the Target Animal and Effectiveness

This section sets forth the effectiveness and target animal safety data needed for the approval of NADA's for sulfonamide products within the scope of the DESI program. These requirements apply to NADA's that are covered by interim marketing privileges under § 510.450, and to future NADA's. Interim marketing and future NADA's with claims not listed in section VII below will have to be supported by adequate and well-controlled investigations before they can be approved.

Sulfamethazine, sulfaquinoxaline, sulfamerazine, and sulfathiazole were evaluated as part of the DESI program. The products were evaluated as "probably effective" and on the basis of published literature and labeling revisions were moved to the "effective" category by FDA for the claims and species listed below in section VII.

The DESI-reviewed sulfamethazine and sulfaquinoxaline products listed below are presently the subject of approved NADA's and are marketed for these uses. Sponsors of NADA's for identical or similar products have several options, as discussed in detail below, for submitting data to show bioequivalency of their products with the appropriate DESI-reviewed drug. Sponsors may submit data from blood level studies comparing their products with the appropriate DESI-reviewed product. In the alternative, sponsors may establish bioequivalency by demonstrating the bioavailability (serum or plasma of blood) of their products, or by demonstrating through in vivo clinical studies the effectiveness of their products for one of the indications that will be on the label.

Normally the agency would require the sponsors of products that are identical or similar to the DESI-reviewed suflamethazine and sulfaquinoxaline products to establish bioequivalency through blood level comparisons with the DESI-reviewed product. However, as discussed below, sponsors of the other four sulfonamides within the scope of this notice must by necessity conduct bioavailability or clinical studies. Therefore, the agency has decided in the interest of fairness to made these options available to sulfamethazine and sulfaquinoxaline sponsors. (The discussion below with respect to cattle, swine, sheep, and rabbits does not mention clinical studies because it is anticipated that bioavailability blood level studies will be more easily accomplished. Sponsors may conduct clinical studies, however. Also, as explained below, bioavailability data are not appropriate for poultry.)

Because the sulfathiazole and sulfamerazine products reviewed by NAS/NRC are no longer being marketed, it will not be possible for sponsors of identical or similar products to demonstrate bioequivalency by comparison with the DESI-reviewed products. Although products containing sulfapyridine and sulfanilamide were marketed for many years before 1962, the products were not the subject of approved NADA's and were not submitted for review by NAS/NRC. In view of the existence of interim-marketing privileges for drug products containing these sulfonamides, and in the interest of applying the same general data submission requirements to all sponsors of interim-marketing sulfonamide NADA's FDA has concluded that the products listed below should be treated as having been reviewed by NAS/NRC as part of the DESI program. The agency has reviewed publicly available literature and has concluded that these two drugs are safe to the target animal and effective for the uses listed below. (A list of these references is available at the Dockets Management Branch (address above).) Sponsors of NADA's for these four sulfonamides should submit, as discussed below, either bioavailability (blood level) data or data from in vivo clinical studies.

FDA has concluded that NADA's for drug products containing more than one sulfonamide will comply with the Center for Veterinary Medicine's combination drug policy (21 CFR 514.1(b)(8)(v)) without submission of data from studies that compare the combination of sulfonamides with the individual sulfonamides. Because all sulfonamides have the same mechanism of action, each individual sulfonamide can be expected to contribute to the total effect of the combination drug.

Different data requirements apply depending on species. Regarding the animal species and uses listed below, the agency has divided all species into two groups. One group of species includes cattle, swine, sheep, and rabbits; the other group includes chickens and turkeys. Satisfactory bioequivalency, bioavailability (blood level), or clinical studies conducted in one animal species will be sufficient to satisfy that requirement for that specific drug product with respect to other animal species.

Adequate and well-controlled studies that meet the requirements of the act and regulations will be required for any claims, species, or conditions of use not listed below. FDA will comment, upon request, on any protocols proposed to establish safety and effectiveness. Questions should be addressed to the contact person listed above.

The subsections below describe in general terms the characteristics of the bioequivalency, bioavailability, or clinical studies that are required. Sponsors are advised to consult the Center for Veterinary Medicine through the contact person named above for additional guidance.

A. Cattle, Swine, Sheep, and Rabbits

1. Sulfamethazine and sulfaquinoxaline: Data to show bioequivalency with the DESI-reviewed product (47 FR 25320; June 11, 1982 and 48 FR 3902; January 28, 1983) should be obtained using a 10 x 10 crossover study with a resting period of 2 to 4 weeks. In the alternative, FDA will accept bioavailability data obtained using a minimum of 10 animals and demonstrating sulfonamide blood levels (serum or plasma of blood) of 6-milligram (mg) percent or more. It is appropriate scientifically to conclude that a sulfonamide drug is bioequivalent to the DESI-reviewed drug, based only on bioavailability data from the test drug, because the therapeutic blood levels of sulfonamides in these species are well established in the published scientific literature (Bevill, R. F., and W. G. Huber, *Veterinary Pharmacology and Therapeutics*, L. M. Jones, N. H. Booth, and L. E. McDonald, editors, p. 903; Iowa State University Press, 4th ed., 1977).

2. Sulfanilamide sulfamerazine, and sulfapyridine: Bioavailability data should be obtained using a minimum of 10 animals to demonstrate sulfonamide blood levels of 8-mg percent or more.

3. Sulfathiazole: Demonstrated blood levels of 2-mg percent or more using a minimum of 10 animals will be acceptable.

4. Products containing sulfamethazine alone intended solely for intravenous administration are not subject to the requirement for bioequivalency or bioavailability data if the active drug ingredient is in the same solvent and concentration as the DESI-reviewed product (46 FR 62064; December 22, 1981). The sponsor of such a product must submit satisfactory data demonstrating that its product and the DESI-reviewed product are pharmaceutically equivalent. Although the products need not contain the same inactive ingredients, both products must supply equivalent amounts of the active drug ingredient (the same salt or ester of the same therapeutic moiety in the same solvent).

5. Sponsors of pending NADA's for sulfonamide products containing two or more sulfonamides must submit bioavailability data demonstrating sulfonamide blood levels (serum or plasma of blood) of 6-mg percent or more. A minimum of 10 animals should be used in determining such blood levels.

B. Chickens and Turkeys

1. Sulfamethazine or sulfaquinoxaline alone in the form of a drinking water solution or soluble powder: A study to show bioequivalency with the DESI-reviewed drug (47 FR 25320; June 11, 1982 and 48 FR 3902; January 28, 1983) should use 28 pens of 10 chickens or turkeys between 3 and 4 weeks of age. An extra 10 birds receiving the same diet and untreated water should be sacrificed to determine "background" sulfonamide blood levels and to generate recovery data. The dosage and length of treatment should be identical to those listed below for the drug product. At 2, 4, 8, 12, 16, 24, and 48 hours after dosing, two pens per treatment group should be selected randomly and the birds sacrificed and samples collected by exsanguination. Blood levels over time should be compared by analyses of variance with regard to areas under the curves, average peak heights, and overall split-plot analysis in time. The last analysis is intended to compare overall mean blood levels as well as the slopes of the blood level curves.

In the alternative, the results of a clinical study demonstrating the effectiveness of the drug against one disease claimed in the suggested labeling may be submitted. The study should consist of 80 birds in 8 experimental batteries of 10 birds each. All of the birds should be infected, with one-half of the battery birds medicated and the other half not medicated. FDA suggests that protocols be submitted together with the proposed method of statistical analysis for FDA comment before initiating the studies. FDA is providing for a clinical study rather than a bioavailability study because of the lack of adequate data concerning therapeutic blood levels of sulfonamides in poultry.

2. Sulfamerazine alone in the form of a drinking water solution or soluble powder: No NADA's for such products were filed under the provisions of § 510.450. Future sponsors of NADA's with the acceptable claims listed below should submit the results of a clinical study, as discussed in section III.B.1.

3. Sulfathiazole, sulfanilamide, and sulfapyridine: No NADA's were filed for any of these products alone for use in chickens or turkeys under the provisions of § 510.450. FDA does not have any data supporting the safe and effective use of these sulfonamides in poultry. Sponsors who desire to submit future NADA's for these products will have to submit data from adequate and well-controlled studies that meet the requirements of the act and regulations, and are advised to contact the contact person listed above.

4. Combinations of sulfamerazine, sulfamethazine, and sulfaquinoxaline: The results of a clinical study, as discussed under section III.B.1. above, should be submitted.

IV. Other Data Required for Approval of NADA's

Information required by § 514.1 concerning manufacturing facilities and controls, and stability data should be submitted by all sponsors. Sponsors of interim marketing NADA's should update information that is not current. Sponsors may be exempt from the submission of certain environmental data in accordance with § 25.1(f)(2) (21 CFR 25.1(f)(2)). Environmental impact analysis regarding manufacturing processes is required in accordance with § 25.1(g)(2) (21 CFR 25.1(g)(2)). A satisfactory freedom of information summary must be submitted in accordance with § 514.11(e)(2)(ii) (21 CFR 514.11(e)(2)(ii)).

V. Termination of Interim Marketing

This action is part of the agency's effort to terminate in an orderly and timely fashion the interim marketing privileges of drugs under § 510.450. Sponsors of such drugs must submit a statement of intent by October 3, 1984, and the data described above and revised labeling by October 7, 1985. After that time, NADA's that are deficient in one or more categories will be subject to prompt administrative action.

After the agency has reviewed the data and revised labeling submitted in response to this notice, it will publish a proposal to revoke § 510.450. FDA will take action on each NADA covered by interim marketing, and will either approve it or publish a notice of opportunity for hearing on denial of approval (21 CFR 514.111). Hearings will be held if justified. After a final rule revoking § 510.450 becomes effective, any sulfonamide-containing drug on the market intended for use in food-producing animals that is not the subject of an approved NADA will be in violation of the act and subject to regulatory action, unless covered by a statutorily provided exception to the requirement of an NADA.

VI. List of Firms Having NADA's Subject to § 510.450

The firms listed below are sponsors of NADA's for products being marketed under § 510.450. Veterinary Laboratories, Inc., submitted NADA's under its own name and has assumed the sponsorship of NADA's formerly held by Veterinary Products Corp.

1. Cadco, Inc., P.O. Box 3599, 10100 Douglas Ave., Des Moines, IA 50322.
2. Fort Dodge Laboratories, Fort Dodge, IA 50501.
3. Franklin Laboratories, 1777 South Bellaire St., Denver, CO 80222.
4. Frank Veterinary Laboratories, 7239 Washington Ave. South, Edina, MN 55435.
5. International Multifoods Corp. (formerly Osborn Laboratories), 1200 Multifoods Bldg., 8th and Marquette Sts., Minneapolis, MN 55402.
6. Masti-Kure Products Co., Inc., 168 Yantic St., Norwich, CT 06360.
7. Medico Industries, Inc., Elkan Estates, P.O. Box 338, Elwood, KS 66024.
8. Merck Sharp & Dohme Research Laboratories, Rahway, NJ 07065.
9. M & M Livestock Products Co., Eagle Grove, IA 50533.
10. Norden Laboratories, Inc., Lincoln, NE 68501.
11. Pfizer, Inc., 235 East 42d St., New York, NY 10017. (NADA's formerly held by Rachelle Laboratories, Inc.).
12. Philips Roxane, Inc., 2621 North Belt Highway, St. Joseph, MO 64502.
13. Quality Plus Products Corp., 2110 6th Ave. South, Fort Dodge, IA 50501.
14. Ralston Purina Co., Checkerboard Square, St. Louis, MO 63188.
15. Rhone-Poulenc, Inc., (formerly Hess & Clark Division of Rhodia, Inc.), P.O. Box 125, Black Horse Lane, Monmouth Junction, NJ 08852.
16. I. D. Russell Co. Laboratories, 2465 Harrison St., Kansas City, MO 64108.
17. Salsbury Laboratories, Charles City, IA 50616.
18. Syntex Laboratories, Inc., (Synthex/Diamond Laboratories), 3401 Hillview Dr., Palo Alto, CA 94304.
19. Vet-A-Mix Laboratories, Inc., P.O. Box 88, Shenandoah, IA 51601.
20. Veterinary Laboratories, Inc., (formerly Veterinary Products Corp.), 12340 Santa Fe Dr., Lenexa, KS 66215.
21. Vineland Laboratories, 2285 East Linder Ave., Vineland, NJ 08360.
22. Vista Laboratories, Inc., Christiansted, St. Croix, Virgin Islands.
23. Wendt Laboratories, Inc., 100 Nancy Dr., Belle Plaine, MN 56011.
24. Veterinary Laboratories, Inc., (formerly Wittney & Co.,) 4055 Colorado Blvd., Denver, CO 80216.

VII. Drug Products Containing One or More Sulfonamides

Listed below in this section are the products containing one or more of the sulfonamides within the scope of this notice, without other active ingredients, that have been reviewed by FDA, along with the claims that FDA has concluded are effective. The names of the sponsors, NADA numbers, and product names for products currently being marketed under § 510.450 are also listed. Drug products containing sulfonamides and other ingredients are listed in section VIII.

For combination drugs containing two or more sulfonamides, the acceptable disease claims are limited to those that are common to the acceptable claims for the individual sulfonamides in the combination. In the list of drug products below, a combination product appears under the heading of the individual sulfonamide in the combination product with the fewest claims.

The existing labeling of some interim-marketed products containing more than one sulfonamide does not conform to the acceptable claims for the particular combination of sulfonamides. These products are indicated with a (+) below. Sponsors may reformulate all sulfonamide-containing products that are covered by interim marketing under § 510.450. For example, sulfathiazole could be removed from a product containing sulfamerazine, sulfamethazine, sulfathiazole, and sulfaquinoxaline that is intended for use in poultry, because FDA has concluded that poultry is not an acceptable species for sulfathiazole. In the alternative, poultry could be deleted from the list of intended species. If a product is reformulated, the sponsor should submit the required information for the reformulated product within the time permitted by this notice.

If the sponsor of an NADA under § 510.450 does not agree with FDA's conclusion that reformulation or labeling changes are necessary, the sponsor should either submit complete safety and effectiveness data, as discussed above, or request a hearing on denial of approval. Sponsors of future NADA's for combination products with claims that are not limited to those that FDA has concluded are acceptable wil need to submit complete safety and effectiveness data.

A. Sulfamethazine

1. Accepted disease claims:

Species

Cattle: For the treatment of bovine respiratory disease complex (shipping fever complex) associated with *Pasteurella* spp.; bacterial pneumonia associated with *Pasteurella* spp.; nectrotic pododermatitis (foot rot) and calf diphtheria caused by *Fusobacterium necrophorum.* Colibacillosis (bacterial scours) caused by *Escherichia coli;* coccidiosis caused by *Eimeria bovis* and *E. zurnii;* acute mastitis caused by *Streptococcus* spp.; acute metritis caused by *Streptococcus* spp.

Swine: For the treatment of bacterial pneumonia associated with *Pasteurella* spp.; porcine colibacillosis (bacterial scours) caused by *Escherichia coli.*

Sheep: For the treatment of pasteurellosis caused by *Pasteurella* spp.; bacterial pneumonia associated with *Pasteurella* spp.; colibacillosis (bacterial scours) caused by *Escherichia coli.* For the control and treatment of coccidiosis caused by *Eimeria ovinoidalis (Eimeria ninakohlyakimovae).*

Chickens: For the ocntrol of infectious coryza caused by *Hemophilus gallinarum;* coccidiosis caused by *Eimeria tenella* and *E. necatrix;* acute fowl cholera caused by *Pasteurella multocida;* pullorum disease caused by *Salmonella pullorum.*

Turkeys: For the control of coccidiosis caused by *Eimeria meleagrimitis. E. adenoeides.*

Dosage

Cattle, sheep, and swine (soluble powder and drinking water solution 12.5 percent)—oral.

Cattle and sheep (bolus). Initially 1½ grain per pound body weight (equivalent to 97.2 mg per pound body weight) followed by ¾ grain per pound body weight (equivalent to 48.6 mg per pound body weight) every 24 hours. Do not exceed 5-day treatment. Dosage can be rounded to initially 100 mg per pound body weight, followed by 50 mg per pound body weight every 24 hours.

Cattle (injectable solution 25 percent). Initially 1½ grain per pound (equivalent to 97.2 mg per pound body weight) followed by ¾ grain per pound (equivalent to 48.6 mg per pound body weight) every 24. hours. Dosage can be rounded to initially 100 mg per pound body weight followed by 50 mg per pound body weight every 24 hours.

Chickens and turkeys (soluble powder). Prepare a 12.0-percent stock solution. Add 1 fluid ounce to each gallon of drinking water or one gallon of the stock solution to 128 gallons of drinking water. This will provide a recommended dosage of approximately 58 to 85 mg per pound per day of the drug in chickens and approximately 80 to 124 mg per pound per day in turkeys depending upon the dosage, age, and class of chicken or turkeys, ambient temperature, and other factors.

Indications	Control
Infectious coryza (chickens).	Medicate for 2 consecutive days.
Acute fowl cholera (chickens).	Medicate for 6 consecutive days.
Pullorum disease (chickens).	Medicate for 6 consecutive days.
Coccidiosis (turkeys and chickens).	Medicate for 2 days then reduce drug concentration to one half above 4 additional days.

Drinking Water Solution 12.5%. Add 1 fluid ounce to each gallon of drinking water or 1 gallon of drinking water solution 12.5 percent to 128 gallons of drinking water. This will provide approximately 61 to 89 mg per pound per day of the drug in chickens and approximately 53 to 130 mg per pound per day in turkeys, depending upon dosage, age, and class of chickens or turkeys, ambient temperature, and other factors.

Indications	Control
Infectious coryza	Medicate for 2 consecutive days.
Acute fowl cholera.	Medicate for 6 consecutive days.
Pullorum disease	Medicate for 6 consecutive days.
Coccidiosis	Medicate for 2 days then reduce drug concentration to one half above 4 additional days.

2. NADA numbers, sponsors, and product names for sulfamethazine alone:

NADA No.	Sponsor	Product name
[illegible]	Vet-A-Mix Laboratories.	Vets-Meth Tablets.
[illegible]-780	Vet-A-Mix Laboratories.	Vets-Meth Solution 12.5%.
[illegible]	Salsbury Laboratories.	Sodium Sulfamethazine 12½%.
[illegible]-047	Salsbury Laboratories.	Sulfamethazine Soluble Powder.
[illegible]	Veterinary Laboratories, Inc. (formerly Vet Products Corp.).	Sulfamethazine 2.5 Gm Boluses.
[illegible]	Veterinary Laboratories.	Sulfamethazine Boluses 15 Grams.
[illegible]-010	Veterinary Laboratories.	Sulfamethazine Sodium Solution 25%.
[illegible]-022	Quality Plus Products.	Sulfamethazine Boluses 15 Grams.
[illegible]	Quality Plus Products.	Sulfamethazine Powder.
[illegible]	Quality Plus Products.	Sodium Sulfamethazine 12½%.
[illegible]	Quality Plus Products.	Sulfamethazine 2.5 Gms.
[illegible]	Quality Plus Products.	Sodium Sulfamethazine 12½%.
[illegible]	Quality Plus Products.	Sulfamethazine Boluses.
[illegible]	Quality Plus Products.	Quality 25% Sodium Sulfamethazine.
[illegible]	Quality Plus Products.	Sodium Sulfamethazine.
[illegible]	International Multifoods (formerly Osborn Laboratories).	Sulfamethazine.
[illegible]	International Multifoods Corp. (formerly Osborn Laboratories).	[illegible] 25%.
[illegible]	International Multifoods Corp. (formerly Osborn Laboratories).	Sodium Sulfamethazine.
[illegible]	[illegible] Products Co., Inc.	Sulfamethazine Bolus.
[illegible]	Quality Plus Products Corp.	Sulfamethazine Sodium Injectable.
[illegible]-077	Quality Plus Products Corp.	Sulfamethazine Boluses 5 Grams.
[illegible]	Vineland Laboratories.	Liquid Vinethazine—25.
100-006	Medico Industries, Inc.	SM-25 Solution.
100-011	Medico Industries, Inc.	SM-25, 25% Solution Sulfamethazine Sodium.
100-014	Medico Industries, Inc.	Sodium Sulfamethazine 12½%.
100-024	Veterinary Laboratories, Inc. (formerly Whitney & Co.).	Sulfamethazine Sulfa Solution 25%.
100-020	Vineland Laboratories.	Vinethazine.
100-071	Frank Veterinary Laboratories.	Frank Sodium Sulfamethazine.
100-096	Wendt Laboratories, Inc.	Sulfamethazine Boluses.
100-126	Vista Laboratories, Inc.	Sulfamethazine Boluses.
100-177	Wendt Laboratories, Inc.	SM-25 Per Cent.
100-179	I. D. Russell Co. Laboratories.	Sodium Sulfamethazine 25 percent.
100-254	Pfizer, Inc.	Sodium Sulfamethazine.

B. Sulfathiazole

1. Acceptable disease claims:

Species

Cattle: For the treatment of bovine respiratory disease complex (shipping fever complex) associated with *Pasteurella* spp.: bacterial pneumonia associated with *Pasteurella* spp.: calf diphtheria and necrotic pododermatitis (foot rot) caused by *Fusobacterium necrophorum:* acute mastitis and acute metritis caused by *Streptococcus* spp.

Swine: For the treatment of bacterial pneumonia caused by *Pasteurella* spp.: porcine colibacillosis (bacterial scours) caused by *Escherichia coli.*

Dosage

Oral—Drinking Water Solution and Soluble Powder.

Cattle and swine: 1½ grain per pound body weight (equivalent to 97.2 mg per pound body weight) per day for 4 days. Do not exceed 4 days' treatment.

Cattle Boluses—Initially 1 grain per pound body weight (equivalent of 64.8 mg per pound body weight) followed by ½ grain per pound body weight (32.4 mg per pound body weight) every 8 hours. Do not exceed 4 days' treatment.

Cattle and swine: Mixtures (two or three) of sulfathiazole, sulfamethazine, or sulfamerazine:

Initially 1 grain per pound body weight (equivalent to 64.8 mg per pound body weight) followed by ½ grain per pound body weight (equivalent to 32.4 mg per pound body weight) every 12 hours. Do not exceed 4 days' treatment.

2. NADA numbers, sponsors, and products containing sulfathiazole alone or in combination with other sulfa products:

NADA No.	Sponsor	Product name
[illegible]	Syntex Laboratories/Diamond Laboratories.	Extra-Sul Boluses. Sulfamethazine sodium. Sulfathiazole sodium.
[illegible]-037	Syntex Laboratories/Diamond Laboratories.	Extra-Sul Solution. Sulfamethazine sodium. Sulfathiazole sodium.
[illegible]	Syntex Laboratories/Diamond Laboratories.	Extra-Sul Powder. Sulfamethazine sodium. Sulfathiazole sodium.
[illegible]	Salsbury Laboratories.	Sulfathiazole sodium sesquihydrate.
[illegible]	Salsbury Laboratories.	Ar-Sulfa Soluble Powder
[illegible]	Salsbury Laboratories.	Sodium Sulfathiazole Soluble Powder.
[illegible]-475	Veterinary Laboratories, Inc. (formerly Vet Products Corp.).	Bi-Sulfa Boluses Improved. Sulfamethazine. Sulfathiazole.
[illegible]	Veterinary Laboratories, Inc. (formerly Vet Products Corp.).	Triple Sulfa Solution 12%. Sulfamethazine sodium. Sulfathiazole sodium. Sulfamerazine sodium.
[illegible]-020	Quality Plus Products.	Triple Sulfa. Sulfamethazine sodium. Sulfathiazole sodium. Sulfamerazine sodium.
[illegible]-027	Quality Plus Products.	Bi-Sulfa Boluses. Sulfamerazine. Sulfathiazole.
[illegible]	Quality Plus Products.	Sulfathiazole Boluses.
[illegible]-041	Franklin Laboratories.	Triple Sulfa 25. Sulfamethazine sodium.

NADA No.	Sponsor	Product name
		Sulfathiazole sodium. Sulfamerazine sodium.
99-044	Franklin Laboratories.	Tri-Sulfa Boluses Improved. Sulfamethazine. Sulfathiazole. Sulfamerazine.
99-047	International Multifoods (formerly Laboratories).	S.G. Seven. Sulfamethazine. Sulfathiazole. Sulfamerazine.
+99-052	International Multifoods (formerly Laboratories).	TS 543. Sulfamethazine sodium. Sulfathiazole sodium. Sulfamerazine sodium.
99-059	Fort Dodge Laboratories.	Sentisul 12.5% Sulfamethazine. Sulfathiazole. Sulfamerazine.
99-075	Quality Plus Products.	Sulfathiazole Sodium N.F.
99-085	Norden Laboratories.	Sulfonse Parenteral. Sulfonamide Solution. Sulfamethazine. Sulfathiazole.
99-093	Philips Roxane, Inc.	Anchor Sul-Thiazole. Sodium sulfathiazole.
99-096	Syntex Laboratories/ Diamond Laboratories.	Extra-Sul Powder. Sulfamethazine sodium. Sulfathiazole sodium.
99-099	Medico Industries, Inc.	Sodium Sulfathiazole.
100-010	Medico Industries, Inc.	Tri-Meth Boluses. Sulfamerazine. Sulfathiazole.
100-019	International Multifoods (formerly Osborn Laboratories).	Sodium Sulfathiazole N.F.
100-023	Rhone-Poulenc, Inc.	Sul-Trel-E.
100-025	Veterinary Laboratories, Inc. (formerly Whitney & Co.).	Tri-Sul 2 MT. Sulfamethazine sodium. Sulfathiazole sodium. Sulfamerazine sodium.
100-069	Wendt Laboratories Inc.	Triad I Boluses. Sulfamethazine. Sulfathiazole. Sulfamerazine.
+100-091	Wendt Laboratories, Inc.	Triple Sulfa Solution 24%. Sulfamethazine sodium. Sulfathiazole sodium. Sulfamerazine sodium.
100-099	Vineland Laboratories.	Thiazole-Sodium. Sulfathiazole sodium.
100-101	Wendt Laboratories, Inc.	Sulfathiazole Boluses.
100-117	Vista Laboratories	Thiazole-Sodium. Sulfathiazole sodium.
100-162	MSD A G VET (Division of Merck & Co., Inc.).	Sul-Thi-Zol. Sulfathiazole sodium.

C. Sulfaquinoxaline

1. Acceptable disease claims:

Species

Sulfaquinoxaline in drinking water or as a drench for cattle and sheep and in drinking water for chickens, turkeys, and rabbits:

Cattle: For the control and treatment of coccidiosis caused by *Eimeria bovis* and *E. zurnii.*

Sheep: For the control and treatment of coccidiosis caused by *Eimeria ovinoidalis (Eimeria ninakohlyakimovae).*

Chickens: For the control of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. maxima,* and *E. brunetti.*

Turkeys: For the control of coccidiosis caused by *Eimeria meleagrimitis* and *E. adenoeides.*

Chickens and turkeys: For the control of acute fowl cholera caused by *Pasteurella multocida* and fowl typhoid caused by *Salmonella gallinarum.*

Rabbits: For the control of coccidiosus caused by *Eimeria stiedae.*

Pheasants and quails: For the control of acute fowl cholera caused by *Pasteurella multocida.*

Dosage

Sulfaquinoxaline 20 percent solution and sulfaquinoxaline 25 percent soluble powder.

Coccidiosis	Control
Chickens (0.04) percent) (0.025 percent).	Give for 2 to 3 days, skip 3 days, then give for 2 more days. If bloody droppings appear, repeat treatment at the level for 2 more days.
Turkeys (0.025 percent).	Give for 2 days, skip 3 days, give for 2 days, skip 3 days, and give 2 more days. Repeat if necessary.
Acute fowl cholera in chickens, turkeys, pheasants, and quail and fowl typhoid in chickens and turkeys (0.04 percent).	Use for 2 to 3 days. Move birds to clean ground. If disease recurs, repeat treatment.

Coccidiosis	Control and treatment
Cattle and feed-lot lambs (0.015 percent).	Give for 3 to 5 days. (Equivalent to 6 mg per pound body weight.)

Medicated Premix

(Concentration in finished feed)

Coccidiosis	Control
Turkeys	0.05 percent for 2 days, follow with 3 days on regular feed and 2 more days on 0.05 percent sulfaquinoxaline feed, again follow with 3 days on regular feed and 2 more days on 0.05 percent sulfaquinoxaline feed. Continue this schedule if necessary until all signs of the outbreak have subsided.
Chickens	0.1 percent for first 48 to 72 hours, skip 3 days; 0.05 percent for 2 days, skip 3 days, 0.5 percent for 2 days. This is a 2-3-2-3-2 schedule. If bloody droppings recur, give 0.05 percent for another 2 days.
Rabbits	0.1 percent for 2 weeks.

Medicated Premix—Continued

(Concentration in finished feed)

Coccidiosis	Control
Acute fowl cholera and fowl typhoid in chickens and turkeys.	0.1 percent for 48 to 72 hours. Mortality should be brought under control. After medication, move birds to clean ground or to a clean house. If disease recurs, use 0.05 percent in feed again for 2 days.

2. NADA numbers, sponsors, and product names for sulfaquinoxaline alone or in combination with other sulfa products:

NADA No.	Sponsor	Product name
99-067	Salsbury Laboratories.	Sulfaquin Medicated Premix.
99-097	Veterinary Laboratories, Inc. (formerly Vet Products Corp.).	Sulquin 333.
—99-629	Quality Plus Products.	Sulfaquinoxaline 3.2%.
99-671	Quality Plus Products.	Sulfaquinoxaline Solution—16 Grams.
99-674	Quality Plus Products.	Sulfaquinoxaline 20% concentrate.
99-676	Quality Plus Products.	Triple Sulfa for Poultry. Sulfamerazine sodium. Sulfamethazine sodium. Sulfaquinoxaline sodium.
100-017	International Multifoods (formerly Osborn Laboratories).	Bovo-Cox Calf Size Boluses. Sulfaquinoxaline.
100-020	International Multifoods (formerly Osborn Laboratories).	Bovo-Cox Boluses. Sulfaquinoxaline.
100-021	International Multifoods (formerly Osborn Laboratories).	Bovo-Cox Powder. Sulfaquinoxaline.
100-022	Rhone Poulenc, Inc. (formerly Hess & Clark).	20% Sulfaquinoxaline Solution.
100-029	Vineland Laboratories.	20% Sulfa-Pol Liquid Concentrate. Sulfamerazine. Sulfaquinoxaline. Sulfamethazine.
100-094	I. D. Russell Co.	Russell Triple Sulfa. Sulfamerazine sodium. Sulfamethazine sodium. Sulfaquinoxaline sodium.
100-169	I. D. Russell Co.	Liquid Sul-O-Nox 3.2%. Sulfaquinoxaline.
+100-174	I. D. Russell Co.	K-Quad Sulfa, Feed Mix 50%. Sulfamerazine. Sulfamethazine. Sulfathiazole. Sulfaquinoxaline.
100-175	I. D. Russell Co.	Liquid Sul-O-Nox 3.2% and 20% Sulfaquinoxaline.
100-176	I. D. Russell Co.	Liquid Sul-O-Nox 34.44% Sulfaquinoxaline.

D. Sulfamerazine

1. Acceptable disease claims:

Species

Cattle: for the treatment of bovine respiratory disease complex (shipping fever complex) associated with *Pasteurella* spp.; bacterial pneumonia associated with *Pasteurella* spp.;

colibacillosis caused by *Escherichia coli*; necrotic pododermatitis (foot rot) and calf diphtheria caused by *Fusobacterium necrophorum*; coccidiosis caused by *Eimeria bovis* and *E. zurnii*.

Sheep: For the treatment of bacterial pneumonia associated with *Pasteurella* spp.; colibacillosis caused by *Escherichia coli*.

Swine: For the treatment of bacterial pneumonia associated with *Pasteurella* spp.; colibacillosis caused by *Escherichia coli*.

Chickens: For the control of infectious coryza caused by *Hemophilus gallinarum*; coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. maxima, E. brunetti*, acute fowl cholera caused by *Pasteurella multocida*; pullorum disease caused by *Salmonella pullorum*; fowl typhoid caused by *Salmonella gallinarum*.

Turkeys: For the control of coccidiosis caused by *Eimeria adenoeides* and *E. meleagrimitis*; acute fowl cholera caused by *Pasteurella multocida*; fowl typhoid caused by *Salmonella gallinarum*.

Dosage—Orally

Cattle, sheep, and swine: Initially 1 grain per pound body weight (equivalent to 64.8 mg per pound body weight) followed by ½ grain per pound body weight every 12 hours. Do not exceed 4 days' treatment.

Chicken and turkeys: 0.1 to 0.2 percent concentration in soluble powder or drinking water solution. Do not exceed 4 days' treatment.

2. NADA number, sponsor, and product name:

NADA No.	Sponsor	product name
100-026	Wendt Laboratories.	Double-44-12.5 percent Solution. Sodium sulfamethazine. Sodium sulfamerazine.

E. Sulfapyridine

1. Acceptable disease claims:

Species

Cattle: For the treatment of necrotic pododermatitis (foot rot) and calf diphtheria caused by *Fusobacterium necrophorum*; bacterial pneumonia caused by *Pasteurella* spp.

Dosage—Orally and injectable

Initially 1 grain per pound body weight (equivalent to 64.8 mg per pound body weight) followed by ½ grain per pound body weight (equivalent to 32.4 mg per pound body weight) every 12 hours. Do not exceed 4 days' treatment.

2. NADA numbers, sponsors, and product names for sulfapyridine alone or in combination with other sulfa products.

NADA No.	Sponsor	Product name
99-604	Philips Roxane, Inc.	Anchor Tri-Sulfa Injectable 24%. Sulfamethazine sodium. Sulfathiazole sodium. Sulfapyridine sodium.
99-606	Veterinary Laboratories, Inc.	Oral Triple Sulfa Solution 25%. Sulfamethazine sodium. Sulfathiazole sodium. Sulfapyridine sodium.
99-608	Veterinary Laboratories, Inc.	Triple Sulfa 150 Solution. Sulfamethazine. Sulfathiazole. Sulfapyridine.
99-609	Veterinary Laboratories, Inc.	Sulfa-Triple No. 4. Sulfamerazine sodium. Sulfathiazole sodium. Sulfapyridine sodium.
99-610	Veterinary Laboratories, Inc.	Sulfapyridine Solution.
99-611	Veterinary Laboratories, Inc.	Triple Sulfa Solution-50. Sulfamethazine. Sulfathiazole. Sulfapyridine.
99-612	Veterinary Laboratories, Inc.	Tri-Sulfa Solution No. 5. Sulfamethazine sodium. Sulfathiazole sodium. Sulfapyridine sodium.
+99-613	Veterinary Laboratories, Inc.	Oral Tri-Sulfa Solution 12%. Sulfamethazine sodium. Sulfathiazole sodium. Sulfapyridine sodium.
99-614	Veterinary Laboratories, Inc.	Sulfapyridine-400.
99-615	Veterinary Laboratories, Inc.	Sulfapyridine Solution.
99-661	Quality Plus Product Corp.	Triple Sulfa-50. Sulfamethazine. Sulfathiazole. Sulfapyridine.
99-665	Quality Plus Products Corp.	Sulfapyridine Solution.
99-676	Quality Plus Products Corp.	Sulfapyridine Solution 12%.
99-679	Quality Plus Products Corp.	Triple Sulfa 4 Injectable. Sulfamethazine sodium. Sulfathiazole sodium. Sulfapyridine sodium.
+99-680	Quality Plus Products Corp.	Triple Sulfa Solution—6 Oral. Sulfamethazine sodium. Sulfathiazole sodium. Sulfapyridine sodium.
99-682	Quality Plus Products Corp.	Oral Triple Sulfa Solution 12%. Sulfamethazine sodium. Sulfathiazole sodium. Sulfapyridine sodium.
99-686	Norden Laboratories, Inc.	Tri-Sulfa G. Sulfamethazine. Sulfathiazole. Sulfapyridine.
+99-691	Philips Roxane, Inc.	Anchor Triple Sulfa Solution 12.5%. Sulfamethazine sodium. Sulfathiazole sodium. Sulfapyridine sodium.
100-002	Wendt Laboratories, Inc.	Neutral Sulfa-7. Sulfamethazine sodium. Sulfathiazole sodium. Sulfapyridine sodium.
100-004	Medico Industries, Inc.	Triple Sulfa Injectable 12%. Sulfamethazine sodium. Sulfathiazole sodium. Sulfapyridine sodium.
100-007	Medico Industries, Inc.	Triple Sulfa Injectable 24%. Sulfamethazine sodium. Sulfathiazole sodium. Sulfapyridine sodium. Sulfapyridine sodium.
100-013	Medico Industries, Inc.	Sulfapyridine Solution.
100-070	Frank Veterinary Laboratories.	Frank Triple Sulfa Solution [illegible]. Sulfamethazine sodium. Sulfathiazole sodium. Sulfapyridine sodium.
100-079	Frank Veterinary Laboratories.	Frank Triple Sulfa Solution Oral 12%. Sulfamethazine sodium. Sulfathiazole sodium. Sulfapyridine sodium.
+100-082	Wendt Laboratories, Inc.	Oral Triple Sulfa Solution 12%. Sulfamethazine. Sulfathiazole. Sulfapyridine.
100-098	Wendt Laboratories, Inc.	Neutral Sulfa-50 Solution. Sulfamethazine. Sulfathiazole. Sulfapyridine.
100-100	Wendt Laboratories, Inc.	Triad II Solution. Sulfamethazine. Sulfathiazole. Sulfapyridine.
100-102	Wendt Laboratories, Inc.	Sulfapyridine Solution.
100-176	Wendt Laboratories, Inc.	Sulfa-Plex Triple Sulfa Solution Oral 12.5%. Sulfamerazine sodium. Sulfathiazole sodium. Sulfapyridine sodium.

F. Sulfanilamide

1. Acceptable disease claims:

Species

Cattle: For the treatment of bovine respiratory disease complex (shipping fever complex) associated with *Pasteurella* spp.; bacterial pneumonia associated with *Pasteurella* spp.; acute metritis caused by *Streptococcus* spp.; acute mastitis caused by *Streptococcus* spp.

Dosage—Orally

Cattle: Initially 1 grain per pound body weight (equivalent to 64.8 mg per pound body weight) followed by ½ grain per pound body weight (equivalent to 32.4 mg per pound body weight) every 12 hours. Do not exceed 4 days' treatment.

2. NADA numbers, sponsors, and products names for sulfanilamidie alone or in combination with other sulfa products.

NADA No.	Sponsor	Product name
99-651	Salsbury Laboratories.	Sulfanilamide.
99-661	Salsbury Laboratories.	Sulfanilamide Solution.
99-670	Veterinary Laboratories, Inc. (formerly Vet Products Corp.)	Tri-Mam Soln. Sulfanilamide. Sulfathiazole. Sulfamerazine.

NADA No.	Sponsor	Product name
99-880	Veterinary Laboratories, Inc. (formerly Vet Products Corp.).	Tri-Metha-Bolus. Sulfanilamide. Sulfathiazole. Sulfamethazine.
99-931	Quality Plus Products Corp.	Sulfanilamide.
99-934	Quality Plus Products Corp.	Triple Sulfa Boluses. Sulfanilamide. Sulfathiazole. Sulfamethazine.
99-972	Quality Plus Products Corp.	Sulfanilamide Boluses.
99-[illegible]	Philips Roxane, Inc.	Triple Sulfa Bolus. Sulfanilamide. Sulfathiazole. Sulfamethazine.
100-123	Vets Laboratories, Inc.	Triple Sulfa Bolus. Sulfanilamide. Sulfathiazole. Sulfamethazine.

VIII. Combination Drug Products Containing Sulfonamides and Other Ingredients

A. Additional Data Requirements

In additional to the data requirements stated above, sponsors of NADA's for sulfonamides combined with nonsulfonamide drugs, antibiotics, nutrients, or urea must submit complete human food and animal safety and effectiveness data tha meet current standards, as required by § 514.1. The product must meet the combination drug policy set forth in § 514.1(b)(8)(v), except that if the product contains more than one sulfonamide, the mixture of sulfonamide may be considered as one drug for purpose of applying the combination policy. In the alternative, sponsors may request a hearing on denial of approval.

The only exception to the data requirements stated in the immediately preceding paragraph is for products intended for use in drinking water and containing only sulfonamides combined with nutrient components. These products are indicated with an asterisk (*). Sponsors need not comply with the combination drug policy or current human food safety requirements if they comply with the following limitations: Sponsors must demonstrate lack of interference between the nutrients and the drug ingredients. No direct or implied claims for nutrients will be permitted and the trade name of the product may not include the name of such nutrients. Products must bear the followng statement on the label: "The nutrients in this product serve a limited nutritional function only; they have not been shown to have and are not intended to impart any direct therapeutic benefit". Disease claims for these products must be limited to the acceptable claims listed in section VII above under the particular sulfonamide product, or in the case of products containing two or more sulfonamides, to those acceptable claims that are common to the individual sulfonamides in the mixture.

FDA has reviewed available data concerning the use of sulfonamide drugs in combination with urea and acriflavine for intrauterine administration in cattle, sheep, and swine and has concluded that available data do not support any claims for use in such products. There are no approved NADA's for these products. About 10 NADA's for these products were filed under the provisions of § 510.450. In lieu of attempting to substantiate the safe and effective use of these products, sponsors may elect to request a hearing on the denial of approval or may withdraw their applications.

B. New Aninal Drugs Containing Sulfonamides in Combination With Nutrients or Other Drugs

The following new animal drugs containing sulfonamides in combination with nutrients or other drugs are now being marketed under § 510.450:

NADA No.	Sponsor	Product name
*99-780	Philips Roxane, Inc.	Anchor Sulfa Drinking Water Medication. Sulfathiazole sodium. Vitamin A. Vitamin D₃. Ethylenediamine dihydroiodide. Potassium chloride. Calcium gluconate. Sodium bicarbonate. Ferrous sulfate. Zinc sulfate. Cobalt sulfate monohydrate. Manganese sulfate monohydrate. Copper sulfate pentahydrate. Calcium hypophosphite. Magnesium sulfate. Sodium chloride.
*99-[illegible]	Cadco, Inc.	Sulfa-Lyte Medicated. Sulfathiazole sodium. Calcium chloride. Magnesium sulfate. Potassium chloride. Sodium chloride.
*99-843	Salsbury Laboratories.	Hog & Cattle Sulfa with Vitamins, Electrolytes, and EDDI. Sulfathiazole sodium sesquihydrate. Ethylenediamine dihydroiodide. Potassium chloride. Sodium chloride. Sodium carbonate. Vitamin A. Vitamin D₃.
*99-844	Salsbury Laboratories.	Hog & Cattle Sulfa. Sulfathiazole sodium sesquihydrate. Ethylenediamine dihydroiodide. Potassium chloride. Sodium chloride. Sodium carbonate monohydrate.
+*99-845	Salsbury Laboratories.	Triple-Sulfa Solution with Electrolytes. Sulfamethazine sodium. Sulfathiazole sodium. Sulfamerazine sodium. Potassium hydroxide. Sodium hydroxide. Potassium chloride. Sodium chloride. Calcium gluconate.
*99-[illegible]	M & M Livestock Products Co.	Sulfaton Premix. Sulfanilamide. Sulfathiazole. Sulfamerazine. Sulfaquinoxaline. Vitamin A palmitate. D-activated animal sterol (source of Vitamin D₃). Riboflavin. D-Calcium pantothenate. Niacin. Choline chloride. Vitamin B₁₂. Copper oxide. Iron oxide. Manganous oxide. Zinc oxide.
—		Sodium bicarbonate, cobalt carbonate, and potassium iodide.
*99-[illegible]	M & M Livestock Products Co.	M & M V 175. Sulfathiazole sodium. Vitamin A (palmitate). Vitamin D₃. Riboflavin. Niacin. Pantothenic acid. Vitamin B₁₂.
+*99-[illegible]	Salsbury Laboratories.	Triple Sulfa Soluble Powder. Sulfamethazine sodium. Sulfamerazine sodium. Sulfathiazole sodium. Vitamin A. Vitamin D₃. Calcium lactate. Magnesium sulfate. Potassium chloride. Sodium chloride.
*99-[illegible]	Salsbury Laboratories.	Hog and Cattle Sulfa with Vitamins and Electrolytes. Sulfathiazole sodium sesquihydrate. Potassium chloride. Sodium carbonate. Vitamin A. Vitamin D₃.
*99-[illegible]	Vet-A-Mix	Sulectro-Sol-One. Sulfathiazole sodium. Potassium. Sodium present as carbonate, chlorides, citrate, and bicarbonate.
99-[illegible]	Salsbury Laboratories.	Sal-15 Sulfa Soluble with Electrolytes. Sulfamethazine. Sodium. Potassium. Calcium. Magnesium. Chloride.
99-[illegible]	Salsbury Laboratories.	[illegible] Sulfa Solution with Electrolytes. Sulfathiazole. Sulfanilamide. Sulfamethazine. Calcium. Chloride. Magnesium. Potassium. Sodium.
99-884	Salsbury Laboratories.	T-44-P-30 Soluble with Electrolytes. Sulfathiazole. Sulfamethazine. Sulfapyridine. Calcium. Chloride. Magnesium.

NADA No.	Sponsor	Product name
		Potassium. Sodium.
99-865	Salsbury Laboratories.	Triple Sulfa Boluses with Electrolytes. Sulfathiazole. Sulfamethazine. Sulfanilamide. Calcium. Chloride. Magnesium. Potassium. Sodium.
99-866	Veterinary Laboratories, Inc. (formerly Vet Product Corp.).	Sulfa-Urea Bolus. Urea. Sulfanilamide. Sulfathiazole.
99-872	Veterinary Laboratories, Inc. (formerly Vet Product Corp.).	Uterine Boluses with Acriflavine. Urea. Sulfanilamide. Sulfathiazole. Acriflavine.
99-907	Veterinary Laboratories, Inc.	Sulfathiazole Uterine Bolus. Sulfanilamide. Urea.
+ *99-917	Quality Plus Products Corp.	Vi-Sul-Lyte. Sulfathiazole sodium. Sulfamethazine sodium. Sodium, potassium, magnesium, calcium, chlorides, sulfates, and trace elements, iron, cobalt, zinc, copper, and manganese. Vitamin A palmitate. Vitamin D. Riboflavin. Niacinamide. Vitamin B. Ethylenediamine dihydroiodide.
99-918	Quality Plus Products Corp.	Uterine Boluses. Urea. Sulfanilamide. Sulfathiazole.
99-919	Quality Plus Products Corp.	Sulfapyridine-Iodine Boluses. Sulfapyridine. Ethylenediamine dihydroiodide.
99-924	Quality Plus Products Corp.	Uterine Boluses with Acriflavine. Urea. Sulfathiazole. Sulfanilamide.
99-929	Quality Plus Products Corp.	Triple Sulfa 60 with Electrolytes. Sulfamerazine. Sulfathiazole. Sulfamethazine. Calcium chloride. Sodium chloride. Potassium chloride. Magnesium chloride.
*99-933	Quality Plus Products Corp.	Sodium Sulfamethazine 12.5%. Sodium sulfamethazine. Sodium hydroxide. Sodium chloride. Sodium bicarbonate. Potassium chloride. Calcium gluconate and magnesium chloride.
99-938	Franklin Laboratories.	Cattle Scour Boluses. Neomycin sulfate. Sulfamethazine. Pectin. Vitamin A. Vitamin D_3. Attapulgite.
*99-940	Ralston Purina Co.	Purina Electro-cide. Sulfathiazole sodium. Sodium chloride. Sodium iodide. Potassium chloride.
99-942	Franklin Laboratories.	Bacterial Pneumonia Bolus. Sulfamethazine. Ethylenediamine dihydroiodide. Chloride salts of sodium. Calcium. Magnesium. Potassium. Trace minerals of iron, cobalt, copper, magnesium, and zinc.
99-943	Franklin Laboratories.	Bacterial Scour Boluses. Sulfamethazine. Neomycin. Homatropine methylbromide. Attapulgite activated.
99-945	Franklin Laboratories.	Foot Rot Boluses. Sulfapyridine. Ethylenediamine dihydroiodide.
99-946	Franklin Laboratories.	Calf Bacterial Scour Treatment Solution. Cattle Scour Treatment Solution. Sulfamethazine. Neomycin. Kaolin. Pectin. Bismuth subcarbonate. Homatropine methylbromide.
+ *99-948	International Multifoods Corp. (formerly Osborn Laboratories).	Hubbard Triple Sulfa Solution. Sulfathiazole sodium. Sulfamethazine sodium. Sulfamerazine sodium. Potassium. Sodium. Magnesium. Calcium and chloride.
99-950	International Multifoods Corp. (formerly Osborn Laboratories).	Triple Sulfa-500 Boluses. Sulfamethazine. Sulfathiazole. Sulfamerazine. Electrolytes.
99-951	International Multifoods Corp. (formerly Osborn Laboratories).	Metasul Boluses. Sulfamethazine. Electrolytes.
+ *99-954	International Multifoods Corp. (formerly Osborn Laboratories).	Triple Sulfa with Electrolytes. Sulfamethazine sodium. Sulfathiazole sodium. Sulfamerazine sodium. Sodium, potassium, magnesium, calcium, and chloride.
99-955	International Multifoods Corp. (formerly Osborn Laboratories).	Methapyrin-Stress Formula. Sulfamethazine. Neomycin. Pyrilamine maleate. Methylatropine nitrate. Vitamin A palmitate. Sodium acetate. Potassium acetate. Potassium chloride.
99-957	International Multifoods Corp. (formerly Osborn Laboratories).	Metasul Calf Size Boluses. Sulfamethazine. Electrolytes.
99-958	International Multifoods Corp. (formerly Osborn Laboratories).	Triple Sulfa-030 Boluses. Sulfamethazine. Sulfathiazole. Sulfanilamide. Electrolytes.
99-960	Mast-Kure Products Co., Inc.	Triple Sulfa Tablets with Electrolytes. Sulfamethazine. Sulfathiazole. Sulfanilamide. Sodium bicarbonate. Sodium chloride. Potassium chloride. Calcium dibasic phosphate.
99-961	Mast-Kure Products Co., Inc.	Sulfa Urea Bolus Formula 109. Sulfanilamide. Sulfathiazole. Urea.
99-963	Mast-Kure Products Co., Inc.	Scour-Out for Baby Pigs. Neomycin sulfate. Sulfamethazine. Homatropine methylbromide. Kaolin and psyllium.
99-964	Mast-Kure Products Co., Inc.	MKP Mast-Kure Insertory Formula 206 A. Nitrofurazone. Sulfathiazole. Sulfamethazine. Urea.
99-965	Mast-Kure Products Co., Inc.	Triple Sulfa Bolus with Electrolytes Formula 127. Sulfanilamide. Sulfathiazole. Sulfamethazine. Sodium. Potassium. Chloride. Calcium.
99-966	Mast-Kure Products Co., Inc.	Kendall Calf Scours Tablets Formula 115. Neomycin base. Sulfamethazine. Kaolin. Niacinamide. Vitamin A. Vitamin D.
99-967	Mast-Kure Products Co., Inc.	MKP Giant Liquid-100 Formula 269. Neomycin sulfate. Sulfamethazine. Attapulgite. Pectin.
99-968	Mast-Kure Products Co., Inc.	Mast-Kure Kalf-Caps Formula 146. Neomycin sulfate. Sulfamethazine. Kaolin. Pectin.
*99-979	Quality Plus Products Corp.	Sulyte Powder. Sodium sulfathiazole. Sodium. Potassium. Calcium. Magnesium. Chloride. Ethylenediamine dihydroiodide.
+ *99-981	Quality Plus Products Corp.	Triple Sulfa with Electrolytes. Sulfathiazole sodium. Sulfamerazine sodium. Sulfamethazine sodium. Potassium. Calcium. Magnesium. Sodium. Chloride. Gluconate. Bicarbonate.
*99-983	Vineland Laboratories.	Triple Sulfa with Electrolytes. Sulfamethazine sodium. Sulfathiazole sodium. Sulfamerazine sodium. Sodium. Potassium. Calcium. Magnesium as chloride, carbonate, sulfate, and lactate, plus trace amount of cobalt, zinc, copper, manganese, and iron.
99-984	Norden Laboratories, Inc.	Sulfa-Urea Boluses. Sulfanilamide. Sulfathiazole. Urea.
99-987	Norden Laboratories, Inc.	Sulkamycin S Boluses. Sulfamethazine. Neomycin.
99-988	Norden Laboratories, Inc.	Sulkamycin-S Powder. Sulfamethazine. Neomycin sulfate.
99-990	Philips Roxane, Inc.	Anchor Sulfa Urea Boluses. Urea. Sulfanilamide. Sulfathiazole.
99-992	Philips Roxane, Inc.	Anchor Uterine-Care Boluses. Sulfanilamide. Urea.

NADA No.	Sponsor	Product name
100-001	Medco Industries, Inc.	TMP-160 Improved Boluses. TMP-40 Improved Boluses. Sulfathiazole. Sulfamethazine. Sulfapyridine. Calcium chloride. Magnesium. Potassium. Sodium.
◆*100-003	Wendt Laboratories, Inc.	Merasol Soluble Powder. Sulfamerazine sodium. Sulfathiazole sodium. Vitamin A palmitate. Ethylenediamine dihydroiodide. Sodium acetate. Sodium chloride. Potassium chloride. Magnesium sulfate. Calcium lactate.
◆*100-005	Medco Industries, Inc.	Medsol Soluble Powder. Sulfamerazine sodium. Sulfathiazole sodium. Ethylenediamine dihydroiodide. Vitamin A palmitate. Potassium acetate. Sodium acetate. Sodium chloride. Potassium chloride. Magnesium sulfate. Calcium lactate.
100-009	Medco Industries, Inc.	SM-30 Boluses. SM-5 Boluses. SM-30 Boluses. Sulfamethazine. Sodium. Potassium. Calcium. Magnesium. Chloride ions.
100-012	Medco Industries, Inc.	Su-Neo-Vet (Calf Scour Bolus). Neomycin. Sulfamethazine. Sulfathiazole. Atropine. Vitamin A.
100-015	Medco Industries, Inc.	Triple Sulfa Improved Boluses. Sulfathiazole. Sulfamethazine. Sulfamerazine. Calcium. Chloride. Magnesium. Potassium. Sodium.
100-016	International Multifoods Corp. (formerly Osborn Laboratories).	Methagyrin Boluses. Sulfamethazine. Neomycin. Pyrilamine maleate. Methylatropine Nitrate. Vitamin A. Electrolytes.
*100-018	International Multifoods Corp. (formerly Osborn Laboratories).	Supersweet-Solyte. Sulfathiazole sodium. Ethylenediamine dihydroiodide. Sodium. Potassium. Calcium. Magnesium. Iron as chlorides plus trace minerals and vitamins.
*100-027	Vineland Laboratories.	Sulfa-Pol-Plus TA Soluble Concentrate. Sulfamethazine sodium. Sulfamerazine sodium. Sulfaquinoxaline sodium. Thiamine hydrochloride. Vitamin A palmitate.
*100-030	Cadco, Inc.	12½% Liquid Sulfamethazine. Sulfamethazine sodium. Potassium. Sodium. Calcium. Magnesium.
		[illegible] (chloride sulfate).
◆*100-031	Cadco, Inc.	Triple Sulfa Solution with Electrolytes. Sulfamethazine sodium. Sulfathiazole sodium. Sulfamerazine sodium. Sodium hydroxide. Sodium chloride. Sodium bicarbonate. Potassium chloride. Calcium gluconate. Magnesium chloride.
◆*100-0[illegible]	Wendt Laboratories, Inc.	Treat Drinking Water Solution. Sulfamethazine sodium. Sulfathiazole sodium. Sulfamerazine sodium. Sodium hydroxide, sodium chloride, sodium bicarbonate, potassium chloride, calcium chloride, and magnesium sulfate.
100-057	Wendt Laboratories, Inc.	Sulfa-Urea Boluses. Sulfathiazole. Sulfamethazine. Urea.
*100-098	Vineland Laboratories.	Triple Sulfa with Electrolytes. Sulfamethazine sodium. Sulfathiazole sodium. Sulfamerazine sodium. Sodium. Potassium. Calcium. Magnesium. Iron occurring as a chloride, carbonate, sulfate, phosphate, and lactate plus trace of cobalt, zinc, copper, and manganese.
100-116	Vista Laboratories, Inc.	Sulfamethazine Boluses with Electrolytes. Sulfamethazine. Potassium. Calcium. Magnesium. Sodium. Trace elements, cobalt, zinc, manganese, copper, and iron.
100-122	Vista Laboratories, Inc.	Triple sulfa Boluses with Electrolytes. Sulfanilamide. Sulfathiazole. Sulfamethazine. Potassium, calcium, magnesium sodium and elements, cobalt, zinc, manganese, copper, and iron.
*100-160	International Multifoods Corp. (formerly Osborn Laboratories).	Mer-A-Lite Soluble Powder. Sulfathiazole sodium. Potassium acetate. Sodium acetate. Sodium chloride. Potassium chloride. Magnesium sulfate. Calcium lactate.
100-161	International Multifoods Corp. (formerly Osborn Laboratories).	Med-A-Sol. Sodium sulfathiazole. Sodium [illegible] dihydrate. Vitamin A (as palmitate). Vitamin D. Menadione sodium bisulfite. Calcium pantothenate. Niacin. Riboflavin. Thiamine hydrochloride. Ethylenediamine dihydroiodide. Potassium acetate. Sodium acetate. Sodium chloride. Potassium chloride. Magnesium sulfate and calcium lactate.
*100-162	Cadco, Inc.	Hubbard* Sulfa Stress Formula. Soluble powder. Sulfathiazole sodium. Sodium. Potassium. Calcium. Magnesium. Iron occurring as chloride, carbonate, sulfate, phosphate, and gluconate plus trace amounts of cobalt, copper, zinc, and manganese. Ethylenediamine dihydroiodide. Vitamin A palmitate. Vitamin D_3.

IX. Conclusion

This notice informs sponsors of NADA's for sulfonamide products covered by interim marketing under § 510.450 of the information needed for approval of those NADA's After the end of the time period for submitting that information, FDA will take action to conclude in an orderly and timely fashion the interim marketing of sulfonamide products. FDA will either approve interim-marketing NADA's or publish notices of opportunity for hearing on denial of approval.

This notice also informs future sponsors of NADA's for sulfonamide products within the scope of this notice of the data needed to support approval. Sponsors who do not now have interim marketing privileges under § 510.450 may not market products until they have fully approved NADA's.

Dated: June 20, 1984.

Mark Novitch,

Acting Commissioner of Food and Drugs.

[FR Doc. 84-17767 Filed 7-3-84; 8:45 am]

BILLING CODE 4160-01-M

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DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

Office of the Assistant Secretary for Housing—Federal Housing Commissioner

24 CFR Part 201

[Docket No. R-84-1178, FR-1856]

Property Improvement and Manufactured Home Loan Programs

AGENCY: Office of the Assistant Secretary for Housing—Federal Housing Commissioner, HUD.

ACTION: Proposed rule.

SUMMARY: The proposed regulations codify, restate and reorganize the present regulations published in 24 CFR Part 201 which implement Title I.

Question #21

Did CVM receive a ruling from the Office of General Counsel prior to the initiation of the albendazole emergency INAD program stating that the Food, Drug, and Cosmetic Act authorized this program. If so, please provide a copy of that ruling.

Response

CVM did not receive a ruling from the General Counsel's office that the FDC Act authorized this investigational exemption. The initiative to authorize the investigational exemption for albendazole was a management decision in consultation with the Commissioner's office. There is no requirement that the Center obtain rulings from the General Counsel on all of its initiatives.

Question #22

A draft memorandum of FDA's January 17, 1985, meeting with SmithKline stated: "After the firm's [earlier] conference with Dr. Crawford regarding oncogenesis, etc., reference to safety concerns was excluded from the [albendazole] recall letter. . . Also, Dr. Theorides [a SmithKline scientist] has met with Dr. Crawford (at Cornell) this week to give Dr. Crawford an extensive briefing on carcinogenesis and the pathological significance of the Bio-Dynamics findings." Please provide all memoranda of Dr. Crawford's referenced meetings with the sponsor.

Response

We have no memoranda of contacts between Dr. Crawford and the sponsor other than those that have been provided for the hearing record.

Question #23

Dr. Crawford testified that he called the President of SmithKline one other time besides September 13, 1984, "to tell him to be sure that he was going to receive then a second letter which indicated that [albendazole] had to come off the market." Please state the date of this second call and provide any memorandum that was prepared of it.

Response

A notation of this telephone call was not recorded nor a memorandum prepared. Thus, the exact date of the call cannot be determined.

Question #24

In an October 6, 1982, review of the clorsulon rat carcinogenicity study, the Division of Toxicology found that

> --the incidence of renal tubular adenoma together with adenocarcinomas was higher in the high dose male rats than in the pooled controls;
>
> --the increase in renal tubular adenomas was statistically significant; and
>
> --there was a statistically significant increase in renal epithelial hyperplasia in female rats at the mid and high dose levels.

In a September 21, 1983, review, the Division of Toxicology, after reviewing the historical control data submitted by the sponsor, "confirm[ed] the previous concerns expressed by" the division in its October 6, 1982, review. The September 21, 1983, review stated: "The biological significance of the kidney tumors observed in male and female rats at the mid and high dose levels need clarification from the CAC." However, on September 15, 1983, six days earlier, some members of the toxicology staff met and reportedly

> ". . . agreed with the firm's contention that the occurrence of kidney tubular adenoma observed in the high dose group was not drug-treatment-related and such rare tumors are commonly observed in aging rats. The historical control data submitted by the sponsor (letter dated January 21, 1983) and the data available in open literature in the test species supports the claim of the sponsor. The significant incidence in male rats of kidney epithelial hyperplasia at the mid dose level and hydronephrosis at the high dose level was also discussed at the meeting and it was agreed that these lesions were not pre-neoplastic but were considered as MK-401 treatment-related."

1. Since there is usually an increase in tumors associated with the aging process, what did FDA's toxicologists mean when they concluded the kidney tumors associated with administration of clorsulon were "rare tumors [that] are commonly observed in aging rats"?

2. Please provide the record of FDA's review of the historical control data for kidney tumors in Sprague-Dawley rats provided by the sponsor, as well as that appearing in the literature? In addition, please provide all literature references concerning the incidence of such tumors relied upon by FDA reviewers.

3. If clorsulon's tumorigenic effects on the kidney were not drug-related, how does CVM account for statistically significant tumor increases in treated vs. untreated animals, particularly since clorsulon is structurally related to diuretic drugs [see Dr. Settepani's March 20, 1985, memorandum] known to have an effect on the kidney?

4. Please explain how, without reviewing the kidney slides, FDA was able to conclude that kidney epithelial hyperplasia and hydronephrosis were not pre-neoplastic.

Response

1. The toxicologists were referring to a paper by Anvers, et al. (Expermental Aging Research 8:3-24, 1982). Their data indicate that up to 29 months of age "spontaneously occurring" kidney tumors in the CD rat are very rare but occur more commonally after 29 months of age.

2. This historical control data relied upon by the toxicologists was supplied by Merck, Sharp and Dohme. It consisted of historical control data on CD rats from both Dawson Research Corp. (they conducted the clorsulon studies) and from Merck, Sharp and Dohme's CD rat colony. The historical control data was never reviewed in detail in a written memorandum.

3. The toxicologists reviewing the clorsulon studies agree that the kidney is a target organ and concluded that the kidney pelvic epitheleal hyperplasia in the male and female rat and hydronephrosis in the male rat were drug related.

4. Hydronephrosis is traditionally not considered to be preneoplastic lesion. It is a dilatation of the pelvis due to fluid frequently caused by obstruction of outflow. Hyperplasia may be considered a preneoplastic lesion. It was not considered preneoplastic in the female rats in the clorsulon study because after 29 months on drug there were no signs that the lesion was progressive (i.e., treatment did not lead to tumor formation).

Question #25

On March 13, Dr. Zeeman advised the subcommittee staff that during a January 28 meeting, a Merck representative expressed his expectation that clorsulon would be approved that day. Because clorsulon labels had already been printed, he was not particularly receptive to Environmental Staff's suggestion that stickers be attached to these labels warning of the drug's potential phytotoxicity. Why didn't FDA at least require such warning stickers at the time of approval?

Response

FDA did not require the warning stickers on clorsulon at the time of approval because of the timing of the request (the day before approval). It had not been suggested in earlier reviews and discussion. The first mention of phytotoxicity was made in Dr. Zeeman's review dated November 30, 1984. The review discusses the shortcomings of the phytotoxicity study and disagrees with sponsor's conclusion that clorsulon did not cause phytotoxic effects in oats. No label warning was recommended in the review.

The Center had concluded at that time that clorsulon is a highly effective drug which has been demonstrated to be safe to animal and man by contemporary standards. In the absence of albendazole or clorsulon, cattlemen would resort to using an unapproved chemical and a known carcinogen, hexachlorethane. The Center's decision to allow labeling changes at the first printing was consistent with the extent of the problems identified late in the approval process.

MSD AGVET

Curatrem™

(clorsulon)

8.5% Liver Fluke Drench
for Cattle (85 mg/mL)

32 fl oz (1 quart) 946.4 mL

8636800
Product 24411

Curatrem™ 8.5% Liver Fluke Drench for Cattle (85 mg/mL)
(clorsulon)

Product
24411

FOR ORAL USE IN CATTLE ONLY

INDICATIONS: For the treatment of immature and adult liver fluke *(Fasciola heptica)* in cattle.

DIRECTIONS FOR USE AND DOSAGE: Dose: The recommended dose of CURATREM Suspension is ¼ fl oz per 200 lb body weight (7½ mL per 200 lb or 91 kg). This equals 7 mg clorsulon per kg body weight (approximately 3.2 mg per lb).

Administration: (1) Shake container well before using. (2) Use automatic or single-dose drenching equipment. (3) Set equipment gauge at the required dose. (4) Insert the nozzle of the syringe into the corner of the mouth. (5) Deposit the suspension over the back of the tongue.

Timing of retreatment for cattle is based on geographic, climatic, and husbandry considerations.

Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasitism.

CAUTION: Preliminary tests of eight crop plants (oats, corn, tomatoes, turnips, peas, beans, lettuce, and sunflowers) suggest that manure and urine from treated animals may contain enough clorsulon to cause stunting in pasture and crop plants. Definitive studies on clorsulon plant toxicity and degradation in soil are being conducted.

WARNING: Because a withdrawal time in milk has not been established, do not use in female dairy cattle of breeding age.
Do not treat cattle within 8 days of slaughter.

Keep this and all medications out of the reach of children.

8636901
U.S.Pat. 4064239

Lot No &
Exp Date

MSD AGVET
Division of MERCK & CO., INC.
Rahway, New Jersey 07065, U.S.A.

Question #26

In addition to providing the date that clorsulon labels were modified to include an environmental warning statement, please supply the dates that such labels (1) were submitted to FDA for its approval and (2) went into user distribution channels.

Response

The labels were submitted to FDA for approval on August 14, 1985. The labels went into user distribution channels on April 24, 1985. These dates are reflected in the attached memorandum and letter.

MERCK SHARP & DOHME RESEARCH LABORATORIES
DIVISION OF MERCK & CO., INC.
P.O. BOX 2000, RAHWAY, NEW JERSEY 07065-0914

R. R. BUCK
ASSISTANT DIRECTOR
REGULATORY AFFAIRS

(201) 750-8857

August 14, 1985

Dr. Andrew J. Beaulieu, Director
Division of Surveillance (HFV-210)
Center for Veterinary Medicine
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Beaulieu:

We are writing in response to a telephone call from Dr. Mason today regarding the labeling for our product CURATREM (Clorsulon) 8.5% Liver Fluke Drench for Cattle, NADA 136-742.

As per his request, attached are three copies of our current label for CURATREM which went into use on production material on April 24, 1985. These labels contain the environmental warning statement that Dr. Crawford requested be added at the next printing of labels in his letter of January 29, 1985 (copy attached).

Very truly yours,

Robert R Buck
Robert R. Buck

RECEIVED
85 SEP 5 A9:20
BVM D60

RRB:rfg
Attachment

October 8, 1985
Merck & Co.
Rahway, NJ 07065
DS 9-86
AF 12-84

TO: HFV-210, Dr. Beaulieu

THRU: HFV-214 10/9/85

FROM: R. A. Mason, DVM, PhD, HFV-214

SUBJECT: Clorsulon, NADA 136-742

Per your 10/2/85 request for information on this subject, labeling revised to contain the environmental warning statement requested by CVM was submitted to FDA for approval under cover letter dated August 14, 1985. According to the same covering letter, the revised labels were placed into use on production material on April 24, 1985. A copy of the referenced letter is attached.

R. A. Mason, DVM, PhD

10/8/85

cc: HFV-210, SDRF
HFV-214
RAMason:pcd(34):10-8-85

Question #27

In 1981, Government pathologists concluded that a veterinary drug subject to a pending NADA induced tumors in rat livers. Industry consultants, however, classified these "tumors" as "nodular hyperplasia." Subsequently, an independent peer review group was empanelled, which sided with the Government scientists in characterizing these lesions as tumors. Consequently, in the spring of 1983, the sponsor was advised by FDA that the drug could not be approved. In light of this case, why didn't CVM follow the Cancer Assessment Committee recommendation for an independent review of industry's contention that the liver lesions associated with administration of fenbendazole were "nodular hyperplasia" rather than tumors?

Response

An independent review of the fenbendazole slides was done by Dr. W. R. Brown at the sponsor's request as originally recommended by the Bureau of Foods CAC. Furthermore, the sponsor has recently been requested to submit the slides for FDA/CVM review, in regard to a proposal to add additional claims to the drug's label.

Questions #28

In view of fenbendazole's chemical similarity to albendazole, does FDA plan any further pathology review of the drug, as it has for thiabendazole?

Response

As indicated in our response to question 27, we have made a formal request for the slides on fenbendazole and plan to have our pathologists review them.

Question #29

When FDA decided to suspend regulatory action against feeds containing gentian violet, Dr. Gerald Guest wrote on December 14, 1981, that if safety studies confirmed the agency's suspicions that gentian violet is carcinogenic, regulatory action against poultry feeds containing gentian violet would be reinstituted immediately. FDA's National Center for Toxicological Research (NCTR) concluded that gentian violet causes cancer in animals and should be considered an animal carcinogen. CVM's Cancer Assessment Committee unanimously concurred with this finding last November. In light of NCTR's and CVM's findings of carcinogenicity, why hasn't FDA resumed regulatory action against feeds containing gentian violet?

Response

NCTR has conducted several studies pertaining to the safety of gentian violet. Two studies pertain to the carcinogenicity of gentian violet. The first of these studies was conducted in mice. The preliminary results of the mouse study led CVM to conclude that gentian violet is a carcinogen. The second study was conducted in rats and the results of that study are to be available in the very near future. Additional studies pertain to the levels of residues and metabolites of gentian violet that are likely to persist in edible animal tissue. The results of these studies are currently under review.

The Agency decided that the pathology data in the mouse study should be subject to a data audit. This is a standard operating procedure for compounds tested under the National Toxicology Program. This is not an unusual position for the Agency to take, particularly in the case of carcinogenicity testing where one study can effect the legal status of the tested substance.

When the data audit of the mouse study is complete and the results of the study are considered in light of the residue and metabolite data, the Agency will evaluate what type of regulatory action is appropriate. In light of the fact that there has been a great deal of time-consuming litigation concerning gentian violet over the last 25 years and that even Government victories did not deter manufacturers from continuing to market the product, the Agency may consider that a first step at resolving the issue should involve promulgating a regulation declaring gentian violet to be a food additive and unlawful if not subject to an approved food additive petition. The regulation would have the force and effect of law and could be accomplished in far less time than case-by-case litigation has taken. Once in effect, the regulation would deter not only spurious litigation but also continued product marketing.

Question #30

In an April 9, 1985, memorandum, Dr. Jospeh Settepani wrote that agency attorney, Mr. Fred Degnan, "has never failed to point out that the Agency has a very small burden to successfully defend the position that a sponsored compound is not generally recognized as safe and that this burden appears to be clearly met by the results of the lifetime feeding study with gentian violet in mice." Inasmuch as two agency components have concluded that gentian violet is a carcinogen in at least one mammalian species, what is the legal basis for permitting its continued use in poultry feed?

Response

As stated in the response to question 29, FDA is pursuing a reasoned and consistent course of action with regard to gentian violet. If the data audit confirms the carcinogenicity of this substance, the Agency will move through rulemaking to remove it from poultry feed. Also, see Mr. Drozen's followup response.

Question #31

In January 1985, CVM managers decided that FDA would issue a proposal in the Federal Register to declare gentian violet to be "not GRAS" if it determined that the compound should be prohibited for use in poultry feed. In a February 28, 1985, memorandum, Dr. Settepani wrote that such an option would probably have to be reviewed by the Department and OMB, which is likely to mean that it will be

> ". . . several years or longer before the Center is in a position to remove residues of this carcinogenic dye from our supply. How can we defend these delays to consumers when a much faster option ie., resume taking regulatory action, is available to the center. . . [W]e brought approximately 25 successful seizure actions and two successful injunctions during the 1960s and 70s when we only thought the dye was carcinogenic. Should we do any less now that we know the compound is carcinogenic and we know that residues above the one-in-one million lifetime risk level for cancer occur in the meat from treated birds?"

Why in light of the delays such a proposal could entail, would FDA not merely initiate injunction and/or seizure actions on the grounds that gentian violet is an unapproved and hence illegal food additive when used as a mold inhibitor in poultry feed?

Response

FDA has learned from past attempts that seizure and subsequent litigation first, may not be successful and second, does not seem to have any deterrent effect on the rest of the industry. If the compound is shown to be carcinogenic, the Agency will move through the rulemaking process to remove this substance from poultry feed.

Question #32

In an August 8, 1985, letter to Congressman Raymond J. McGrath, Commissioner Young stated that FDA would not take enforcement action against certain Vitamin K active substances (VKAS) used in animal feed that are neither covered by a prior sanction nor are generally recognized as safe (GRAS). FDA's enforcement plans notwithstanding, please explain how the marketing of these VKAS are consistent with the pre-market approval requirements of the Food, Drug, and Cosmetic Act.

Response

This question assumes that FDA has determined that certain VKAS, other than those that are covered by a prior sanction, are "food additives" as that term is defined at section 201(s) of the Federal Food, Drug, and Cosmetic Act. FDA has not done so. When it asked for data and comments on VKAS in 1976 (41 FR 35009, August 18, 1976), FDA stated that it was considering whether to propose to determine that VKAS are not GRAS but are food additives. FDA opted to terminate the proceedings in 1983 without proposing to determine that VKAS are either food additives or GRAS (see 48 FR 16748, April 19, 1983). To do so would require a resource-intensive rulemaking proceeding. The proceeding would require the issuance of a *Federal Register* proposal, followed by a review of data and comments, and the issuance of a final order in the *Federal Register*. Undoubtedly new information, not available in 1976, would be submitted and would have to be reviewed by FDA.

Even if one assumes for the sake of discussion that the VKAS nonprior sanctioned VKAS are food additive today, the premarketing approval provisions of the Act do not require the FDA to take enforcement action against these substances. Although an unapproved food additive is unsafe under section 409 and adulterated under section 402(a)(2)(c), none of the "prohibited acts" and "penalties" sections of the Act nor any other section of the Act, requires the Agency to take regulatory action against each substance. The Agency's discretion to refrain from taking regulatory action on a case-by-case basis is well established, most recent by the United States Supreme Court in *Heckler* v. *Chaney*, 105 S. Ct. 1649 (1985). Because the Agency has discretion not to act against individual products that are food additives, surely it has discretion not to proceed under its regulation to determine whether a substance is a food additive.

Nearly all nutrient additives for consumption by either man or animal are included in the Agency's GRAS regulations (21 CFR Parts 182 and 582, respectively). While neither GRAS list includes the VKAS, nevertheless VKAS have been added to animal feeds ever since research first demonstrated their need more than 30 years ago. For years, VKAS have been marketed on the basis that they were GRAS or prior sanctioned or both. One notable exception was for the compound menadione demethylprimidinol bisulfite (MPB), marketed by Heterochemical Corporation, which the Agency considered a food additive because of safety concerns with respect to the pyrimidine moiety which is used to improve the stability of the vitamin. Because it is possible that other forms of VKAS could pose similar problems, FDA has requested future marketers of VKAS substances to consult with the Agency before marketing such substances.

Question #33

In an April 9, 1985, memorandum, Dr. Settapani noted that there had been since 1981 a 50% decrease (from 14 to 7) in the number of toxicologists working on animal drug/human food safety issues. In that memorandum, Dr. Settapani wrote:

> ". . . The 50 percent reduction in toxicologists working on HFS [Human Food Safety] . . . has proven to be a real hardship. . . . [T]he center has lost most of its expertise in several areas of toxicology. . . Differences of opinion often arise between drug sponsors and petitioner reviewers concerning interpretation of scientific data. When this happens, sponsors hire the best available experts on the subject to argue their side of the issue. When the Center lacks the necessary expertise to effectively counter these arguments we are in danger of not being able to insure that safe conditions of use of a candidate drug will be established."

Does CVM plan to request additional toxicological resources to carry out its responsibilities? If so, please elaborate.

Response

CVM has recently acquired the services of a genetic toxicologist to fill the need for expertise in in vitro mutagenicity testing. Prior to acquiring this person we utilized the services of FDA scientists at the NCTR to assist us in the review of this data. We are also actively recruiting a Director for the Toxicology Division and are also in the process of recruiting for a staff reviewing toxicologist in the residue toxicology review branch. We recognize that the program staff size was reduced upon its transfer from Foods to CVM and are taking steps to assure sufficient expertise in this area. We plan to add several independent consultants to our roles as assistance to the drug review and bioassay assessments.

Question #34

FDA's current hearing to withdraw the nitrofurans from the market has diverted many agency personnel from other responsibilities. How many FTEs have been allocated to this function?

Response

For the recent nitrofurans hearing eight FTEs were allocated for the preparation and accomplishment of the hearing. These persons were diverted from their regular activities.

From 1981 to April 1983	1.50 FTE
From April 1983 to September 1984	3.50 FTE
From September 1984 to July 1985	2.50 FTE
From July 1985 to August 1985	.32 FTE
From August 1985 to October 1985	.24 FTE
Total FTEs	8.06

Question #35

A June 1980 memorandum from Dr. Robert J. Scheuplein, Director, Food Animal Additives Staff, stated:

> "Because of existing adverse data, it is unlikely that even with additional testing safe conditions of use can be found for Carbadox, Dimetridazole, . . . and Ipronidazole. The approvals for those products are likely to be withdrawn."

Dr. Crawford, in fact, testified that CVM will be addressing the need to initiate administrative action against the approvals of these drugs. How many market withdrawal hearings can CVM convene in a year and carry on the level of activity it currently performs?

Response

CVM can accomplish one complete hearing per year without serious disruption to other necessary activities.

Dr. CRAWFORD. Thank you, Mr. Chairman.

Mr. WEISS. And, again, I want to express my appreciation to you, Dr. Crawford and Dr. Guest, and to the other agency witnesses, for your participation over the course of these last 2 days. Thank you very much.

Dr. CRAWFORD. Thank you, Mr. Chairman, very much.

Mr. WEISS. The subcommittee now stands adjourned subject to the call of the Chair.

[Whereupon, at 1:40 p.m., the subcommittee adjourned, to reconvene subject to the call of the Chair.]

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